2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of 1,1,2,2-tetrachloroethane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure ,inhalation, oral, and dermal; and then by health effect-death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowestobserved- adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death-, or those whose significance to the organism is not entirely clear. A-TSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt

at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the LSE tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of 1,1,2,2-tetrachloroethane are indicated in Table 2-2 and Figure 2-2. Because cancer effects could occur at lower exposure levels, Figure 2-2 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for 1,1,2,2-tetrachloroethane. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute-duration inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute-duration insults, such as

hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

2.2.1.1 Death

A few human deaths have been reported following excessive inhalation exposure to 1,1,2,2-tetrachloroethane. Immediately after World War I, gastrointestinal and neurological distress were reported following occupational exposure to a varnish containing 1,1,2,2-tetrachloroethane that was used to cover fabric airplane wings. Although workers generally recovered (see Section 2), at least 4 of 14 workers later became confused, delirious, comatose, and finally died (Willcox et al. 1915). Autopsies revealed extreme liver destruction and fatty degeneration of the liver. The levels of 1,1,2,2-tetrachloroethane in the air were not measured, so inhaled concentrations that may cause death in humans are not known.

Inhalation of 1,1,2,2-tetrachloroethane has also been shown to cause death in animals. Concentrations of 1,1,2,2-tetrachloroethane in air that cause death in rats following 4-6-hour exposures have been consistently reported to be near 1,000 ppm (Carpenter et al. 1949; Deguchi 1972; Schmidt et al. 1980b; Smyth et al. 1969). Deaths in rats occurred at 5,050 ppm after short (30 minutes) exposures (Price et al. 1978). In mice (Horiuchi et al. 1962; Lazarew 1929; Pantelitsch 1933) and guinea pigs (Price et al. 1978), the level that causes death has been reported to be approximately 5,000-6,000 ppm. In animals surviving more than a few days, fatty degeneration of the liver was seen at necropsy (Horiuchi et al. 1962). All exposures from reliable studies that caused death in rats, mice, and guinea pigs are recorded in Table 2-l and plotted in Figure 2-l.

Table 2-1. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (Sprague-Dawley)	30 min				5050 (3/10 died)	Price et al. 1978
2	Rat (Wistar)	4 hr				1253 M (LC_{50})	Schmidt et al. 1980b
3	Mouse (NS)	3 hr				5900 M (3/10 died)	Horiuchi et al. 1962
4	Gn Pig (Hartley)	30 min				6310 (3/10 died)	Price et al. 1978
	Systemic						
5	Rat (Sprague-Dawley)	30 min	Resp	576		5050 (labored respiration)	Price et al. 1978
			Cardio	5050		6310 (cardiac degeneration in 1/10)	
			Hepatic	6310			
			Renal	6310			
			Endocr	6310			
			Ocular	576	5050 (lacrimation)		
			Bd Wt	6310			
6	Mouse (NS)	3 hr	Hepatic		5900M (congestion and fatty degeneration of the liver)		Horiuchi et al. 1962
7	Mouse (Cb)	3 hr	Hepatic		600 F (increased triglycerides and total lipids and decreased ATP contents in liver)		Tomokuni 1969

Table 2-1. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
8	Mouse (Cb)	3 hr	Hepatic		800 F (increase in liver triglycerides)		Tomokuni 1970
9	Gn Pig (Hartley)	30 min	Resp	576		5050 (labored respiration)	Price et al. 1978
			Cardio	6310			
			Hepatic	6310			
			Renal	6310			
			Endocr	6310			
			Ocular		576 (lacrimation)		
			Bd Wt	6310			
	Neurological						
10	Rat (NS)	6 hr				360 (50% decrease in motor activity)	Horvath and Frantik 1973
11	Rat (Sprague-Dawley)	30 min			576 (reduced activity and alertness)	5050 (narcosis)	Price et al. 1978
12	Gn Pig (Hartley)	30 min			576 (hypoactivity)	5050 (narcosis and tremors)	Price et al. 1978
	INTERMEDIATE EXPOSURE						
	Systemic						
13	Rat (NS)	11 x/29 d 2 d/wk 2 hr/d	Hemato		9000M (decrease in red cell count and hemoglobin content)		Horiuchi et al. 1962
			Hepatic		9000M (congestion and unspecified fatty degeneration of the liver)		
			Bd Wt	9000 M			

Table 2-1. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
14	Rat (Sprague-Dawley)	15 wk 5 d/wk 6 hr/d, then 5 hr/d	Resp	130 F			Truffert et al. 1977
			Hemato	130 F			
			Hepatic		130[b] F (increased liver to body weight ratio; signs of hyperplasia, granulation, and cell vacuolization)		
			Renal	130 F			
			Endocr	130 F			
	Neurological						
15	Rat (NS)	11 x/29 d 2 d/wk 2 hr/d				9000 M (hyperactivity, ataxia, followed by unconsciousness)	Horiuchi et al. 1962

[a]The number corresponds to entries in Figure 2-1.

[b]Used to derive an intermediate inhalation MRL of 0.4 ppm. Concentration converted to an equivalent concentration in humans and divided by an uncertainty factor of 300 (10 for extrapolation from animals to humans, 10 for human variability, and 3 for use of a minimal LOAEL).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Gn pig = Guinea pig; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); NOAEL = no-observable-adverse-effect level; NOS = not otherwise specified; NS = not specified; Resp = respiratory; wk = week(s); wt = weight

Figure 2-1. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Inhalation

Acute (≤14 days)

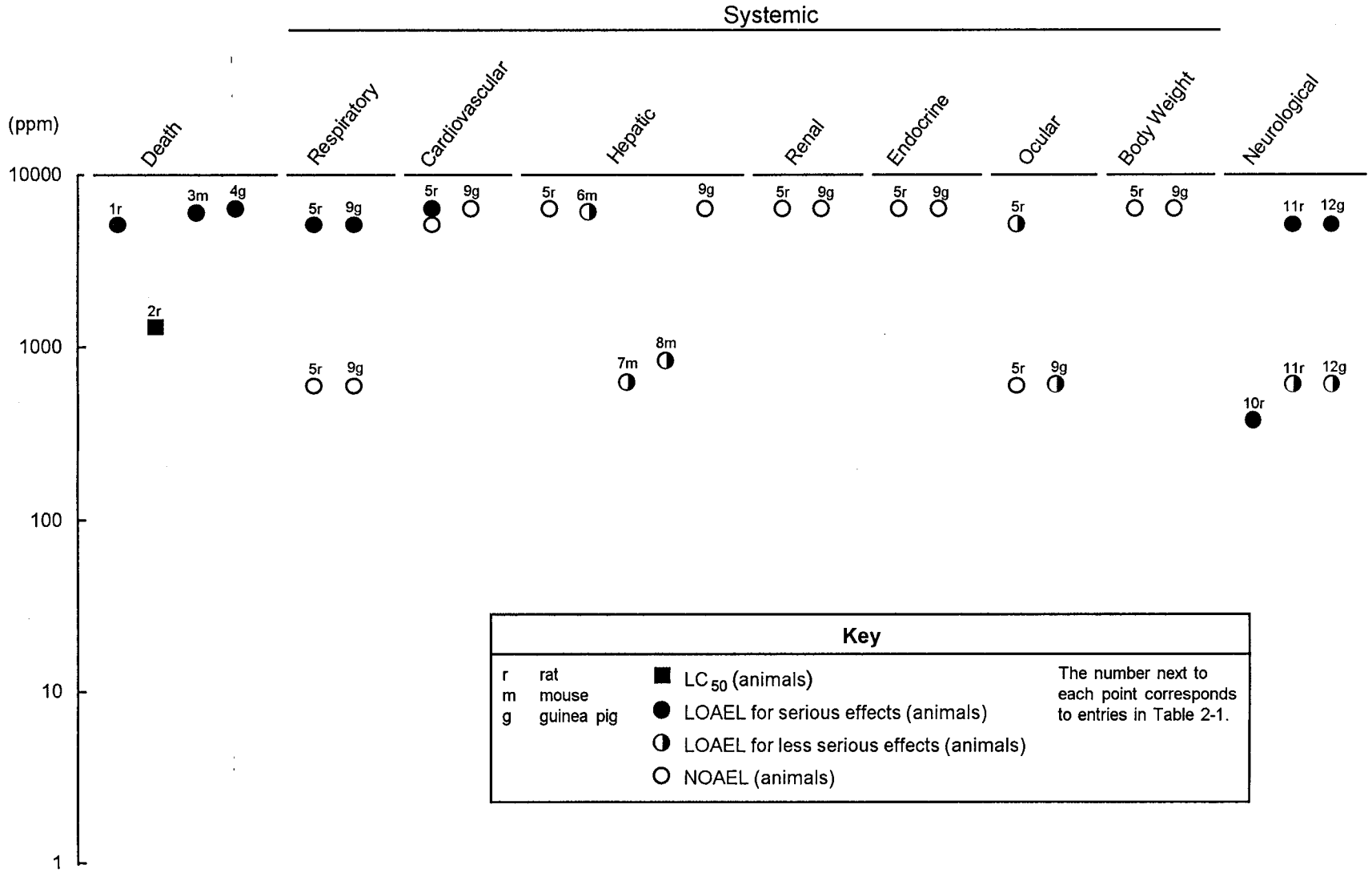
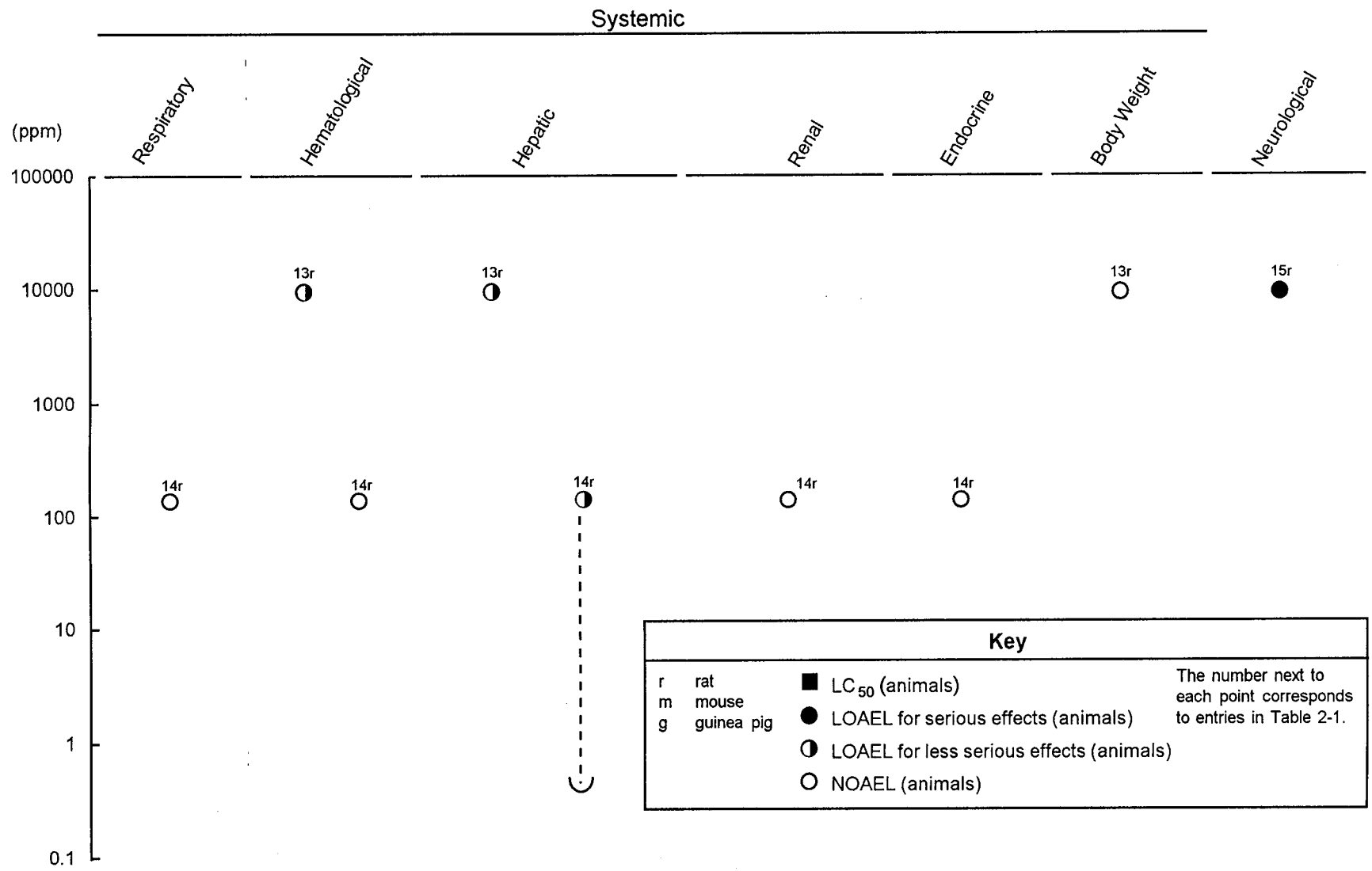


Figure 2-1. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Inhalation

Intermediate (15-364 days)



2. HEALTH EFFECTS

2.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal or dermal effects in humans or animals following inhalation exposure to 1,1,2,2-tetrachloroethane. The systemic effects observed in humans and animals after inhalation exposure to 1,1,2,2-tetrachloroethane are discussed below. The highest NOAEL and all LOAEL values from each reliable study for systemic end points in each species and duration category are recorded in Table 2-1 and plotted in Figure 2- 1.

Respiratory Effects. Minor effects on the respiratory system are caused by 1,1,2,2-tetrachloroethane. At a concentration of 13 ppm, but not 2.9 ppm, mucosal irritation occurred in two humans exposed for 10-30 minutes. Odor was noticed at the lowest concentration tested (2.9 ppm) (Lehmann and Schmidt-Kehl 1936).

Labored respiration was observed in rats and guinea pigs exposed for 30 minutes to 5,050 ppm 1,1,2,2-tetrachloroethane (Price et al. 1978); there was no effect in rats at 576 ppm. Histological examination of the lungs of female rats exposed to 130 ppm intermittently for 15 weeks revealed no treatment-related lesions (Truffert et al. 1977). No histological lesions were found in the lungs of a monkey exposed to 1,974 ppm intermittently for 9 months (Horiuchi et al. 1962). However, only one monkey was studied and a control was not included.

Cardiovascular Effects. Humans exposed to 1,1,2,2-tetrachloroethane in factories showed few, if any, effects on the cardiovascular system. Army workers who were exposed to 1,1,2,2-tetrachloroethane used in a clothing impregnation process showed no increase in deaths due to cardiovascular diseases in a 30-year follow-up period (Norman et al. 1981). Workers exposed to 1,1,2,2-tetrachloroethane in a chemical plant in Italy showed no important clinical changes in cardiovascular function (Gobbato and Bobbio 1968). Exposure levels were not measured in either of these studies.

No pathological changes in rat hearts were found after a 6-hour exposure to 100 ppm (Deguchi 1972). Myocardial damage was found in 1 of 10 rats following exposure to 6,310 ppm for 30 minutes; no such effect occurred in a guinea pig subjected to this same exposure (Price et al. 1978).

No histopathological changes were seen in the heart of a monkey that was exposed to a time-weighted average (TWA) of 1,974 ppm 1,1,2,2-tetrachloroethane vapors 2 hours per day, 6 days per week for

2. HEALTH EFFECTS

9 months (Horiuchi et al. 1962). However, only one monkey was studied, and a control was not included.

Gastrointestinal Effects. Humans exposed to 1 ,I ,2,2-tetrachloroethane in the workplace often developed gastric distress including pain, nausea, vomiting, loss of appetite, and loss of body weight. Such symptoms were found in workers in the fabric airplane wing varnish industry in World War I (Coyer 1944; Willcox et al. 1915), in a penicillin factory in Czechoslovakia (Jeney et al. 1957), and in a jewelry factory in India (Lobo-Mendonca 1963). Although specific complaints were not associated with specific levels of exposure, the exposure levels in the facilities ranged from 1 to 248 ppm. The adverse health effects generally disappeared when the workers left their employment.

Two volunteers who inhaled 1,1,2,2-tetrachloroethane fumes for 10-30 minutes experienced nausea and vomiting after exposure to 2.9 ppm for 20 minutes (Lehmann and Schmidt-Kehl 1936).

Data regarding gastrointestinal effects in animals following inhalation exposure to 1,1,2,2-tetrachloroethane are limited. One monkey exposed to 1,974 ppm 2 hours per day, 6 days per week for 9 months was reported to experience transient diarrhea and anorexia (Horiuchi et al. 1962). However, no control monkey was included.

Hematological Effects. An increase in the number of large mononuclear cells, white blood cells, and platelets, and slight anemia, were found in workers in an artificial silk factory who were exposed to 1,1,2,2-tetrachloroethane vapors (Minot and Smith 192 1). 1,1,2,2-Tetrachloroethane levels were not accurately measured.

Rats exposed to 130 ppm for 15 weeks showed slightly decreased hematocrit levels, but statistical significance was not reported in this study (Truffert et al. 1977). A monkey exposed to 1,974 ppm intermittently for 9 months showed sporadic changes in hematocrit, red blood cell, and white blood cell counts, but these changes showed no clear trend (Horiuchi et al. 1962). At 9,000 ppm, 2 of 3 male rats showed a decrease in red blood cells and hemoglobin content (Horiuchi et al. 1962).

Hepatic Effects. One of the most significant systemic effects of 1,1,2,2-tetrachloroethane is on the liver. Some humans exposed to 1,1,2,2-tetrachloroethane vapors in the workplace have developed jaundice and an enlarged liver (Coyer 1944; Horiguchi et al. 1964; Jeney et al. 1957; Koelsch 1915;

2. HEALTH EFFECTS

Willcox 1915). Specific clinical signs were not associated with specific exposure levels. Vapor concentrations were reported in one study to range from 1.5 to 248 ppm (Jeney et al. 1957).

Liver degeneration, as evidenced by liver congestion and necrosis, was observed in the autopsies of two humans who died after exposure to 1,1,2,2-tetrachloroethane (Willcox et al. 1915). However, one large study showed no significant increases in deaths attributed to liver cirrhosis in over 1,000 men exposed to 1,1,2,2-tetrachloroethane fumes in an Army clothing plant (Norman et al. 1981). Exposure levels were not measured in this study, and the exposure times ranged from about 5 weeks to 1 year.

The liver is also the major target organ for 1,1,2,2-tetrachloroethane toxicity in animals. Mice exposed to 600-800 ppm 1,1,2,2-tetrachloroethane for 3 hours showed fatty changes in the liver (Tomokuni 1969, 1970). Fifty-five female rats exposed to 130 ppm for 5 hours per day, 5 days per week for 15 weeks had increased relative liver weight and signs of hyperplasia (including increased numbers of binuclear cells and appearance of mitoses), granulation, and vacuolization of the liver (Truffert et al. 1977). The LOAEL value of 130 ppm in this study was used to calculate an intermediate-duration inhalation MRL of 0.4 ppm as described in the footnote in Table 2-l and in Appendix A.

No treatment-related histological effects were found in the liver of rats or guinea pigs exposed to 6,310 ppm for 30 minutes (Price et al. 1978). Hepatic effects described as fine-droplet fatty degeneration, inflammatory changes in the liver, and necrotic foci were described in an acute-duration study in which male rats were exposed to 2 ppm 1,1,2,2,-tetrachloroethane for 4 hours per day, for a total of 8 exposures in 10 days (Gohlke and Schmidt 1972). Schmidt et al. (1980b) also observed fine droplet fatty degeneration in the liver when male rats were exposed to 1,1,2,2-tetrachloroethane vapor for four hours. These studies had a number of limitations that obscured interpretation, including maintaining the rats at elevated room temperatures, a lack of a defined dose-response or durationresponse relationship, and inconsistencies in the reported results.

Rats that were exposed to 9,000 ppm for 2 hours per day, 2 days per week for 4 weeks showed fatty livers (Horiuchi et al. 1962). Mice that were exposed to lethal concentrations (up to 6,600 ppm) of 1,1,2,2-tetrachloroethane for 3 hours showed fatty degeneration of the liver (Horiuchi et al. 1962). Rabbits that were exposed to 15 ppm for 7-11 months showed early signs of liver degeneration at necropsy (Navrotskiy et al. 1971). A monkey exposed to a TWA concentration of 1,974 ppm of

2. HEALTH EFFECTS

1,1,2,2-tetrachloroethane for 2 hours per day for 9 months also showed fatty degeneration of the liver (Horiuchi et al. 1962).

Renal Effects. No recent studies were located regarding renal effects in humans following inhalation exposure to 1,1,2,2-tetrachloroethane. Fatty degeneration and congestion of the kidney were found in one female who had died following inhalation of 1,1,2,2-tetrachloroethane over a 2-3-month period (Willcox et al. 1915), but exposure concentrations were not defined.

No treatment-related histological effects were found in the kidneys of rats or guinea pigs exposed to 6,310 ppm for 30 minutes (Price et al. 1978). Similarly, no treatment-related histopathological lesions in the kidney were found in rats exposed to 130 ppm for 15 weeks (Truffert et al. 1977).

Endocrine Effects. No studies were located regarding endocrine effects in humans following inhalation exposure to 1,1,2,2-tetrachloroethane.

A number of end points were assessed in two studies of animals exposed to 1 ,1,2,2-tetrachloroethane, but no effects were found at the highest exposure levels (6,310 and 130 ppm) (Price et al. 1978; Trnffert et al. 1977).

Dermal Effects. No studies were located regarding dermal effects in humans or animals following inhalation exposure to 1,1,2,2-tetrachloroethane.

Ocular Effects. Humans exposed to 1,1,2,2-tetrachloroethane vapors (130 ppm) for 10 minutes experienced ocular mucosal irritation (Lehmann and Schmidt-Kehl 1936). Similarly, guinea pigs exposed to 576 ppm for 5 minutes exhibited eye closure and squinting; by 15 minutes lacrimation was common (Price et al. 1978). Rats showed these effects at 5,050 ppm. These ocular effects are due to direct contact of the eyes with the vapors, rather than a true systemic effect due to inhalation of the vapor. These effects are, therefore, presented in Section 2.2.3.2 on ocular effects.

Body Weight Effects. Humans exposed to 1 ,1,2,2-tetrachloroethane vapors in an occupational setting experienced a 5-15 pound weight loss (Parmenter 1921). However, this weight loss was probably attributable to gastrointestinal disturbances (i.e., nausea, diarrhea, and vomiting) (Parmenter 1921).

2. HEALTH EFFECTS

No effects on body weight were found in several inhalation studies in animals (Horiuchi et al. 1962; Price et al. 1978; Schmidt et al. 1972, 1980b).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans following inhalation exposure to 1,1,2,2-tetrachloroethane.

Rabbits exposed to 1.5 ppm of 1,1,2,2-tetrachloroethane vapor 3 hours per day for 8 months and then immunized with a typhoid vaccine showed a decrease in titers and an increase in the electrophoretic mobility of the specific antibodies when compared to rabbits that were not exposed to 1,1,2,2-tetrachloroethane (Shmuter 1977). No histopathological changes were noted in the spleens of rats which inhaled 100 ppm 1,1,2,2-tetrachloroethane for 6 hours (Deguchi 1972). Since a more complete battery of immune function tests was not performed, this study was not judged to be complete enough to be listed in Table 2-1 or Figure 2-l.

2.2.1.4 Neurological Effects

Human volunteers who inhaled 1,1,2,2-tetrachloroethane (116 ppm and higher for 1 O-30 minutes) reported being dizzy. These effects did not occur when the exposure was 13 ppm (Lehmann and Schmidt-Kehl 1936). Humans exposed to 1,1,2,2-tetrachloroethane fumes in the workplace showed symptoms such as headache, tremors, dizziness, numbness, and drowsiness (Hamilton 1917; Jeney et al. 1957; Lobo-Mendonca 1963; Minot and Smith 1921; Parmenter 1921). Length of exposure was not specifically noted, but the reports seem to indicate that the exposures were generally for a period of about 18 months or less. Exposure levels were only noted in one study, and these ranged from 9 to 98 ppm, with significant skin exposure in addition to the inhalation exposure (Lobo-Mendonca 1963).

In acute-duration experiments, rats showed a decrease in spontaneous motor activity after –being exposed to 360 ppm for 6 hours (Horvath and Frantik 1973) and mice showed a loss of reflexes after being exposed to 1,091 ppm for 2 hours (Lazarew 1929). As the concentration of, or duration of exposure to, 1,1,2,2-tetrachloroethane increased, mice, rats, and guinea pigs showed some combination of a loss of reflexes, loss of spontaneous motor activity, ataxia, prostration, and narcosis (Lazarew 1929; Pantelitsch 1933; Price et al. 1978). Narcosis was also observed in a cat exposed to 8,300 ppm

for 5 hours (Lehmann 1911). One monkey exposed to a TWA of 1,974 ppm of 1,1,2,2-tetrachloroethane for 2 hours per day for 9 months exhibited unconsciousness after each 2 hour exposure, starting at the fifteenth exposure (Horiuchi et al. 1962). Rats exposed to 9,000 ppm for 2 hours per day, twice a day for 4 weeks exhibited hyperactivity, ataxia, and then unconsciousness (Horiuchi et al. 1962).

The highest NOAEL and all LOAEL values from each reliable study for neurological end points in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following inhalation exposure to 1,1,2,2-tetrachloroethane.

Schmidt et al. (1972) reported atrophy of the seminal vesicles and decreased spermatogenesis after 10 days of exposure to 2 ppm 1,1,2,2-tetrachloroethane. They also found that inhalation of the same level (2 ppm) for 38 weeks had no effect on the ability of male rats to sire healthy fetuses. In rats, no effects on the testes, epididymes, ovaries, or uteruses were seen after inhalation exposure for 30 minutes at 6,310 ppm (Price et al. 1978). In female rats, exposure to 130 ppm of 1,1,2,2-tetrachloroethane vapors for 15 weeks also had no effect on the histology of the reproductive organs (Truffert et al. 1977). Lack of histopathology, however, does not indicate that the female can produce appropriate numbers of healthy offspring. Since no mating studies with females exposed to 1,1,2,2-tetrachloroethane vapors were located in the literature, no values for this effect are indicated on Table 2- 1 or Figure 2- 1.

Inhalation of 1,1,2,2-tetrachloroethane for 9 months to a TWA concentration of 1,974 ppm produced no pathological changes in the testes of 1 monkey (Horiuchi et al. 1962).

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans following inhalation exposure to 1,1,2,2-tetrachloroethane.

2. HEALTH EFFECTS

Male rats were exposed to 2 ppm 1,1,2,2-tetrachloroethane 4 hours per day, for an unspecified number of times during a 9-month period. One week before the end of the exposure period, exposed males and control males were mated with unexposed females and the F1 generation was observed for 12 weeks. There was no effect on the number of offspring per litter, neonatal body weight, viability of the offspring, sex ratios, and body weight on day 84. No gross malformations were observed in the offspring (Schmidt et al. 1972).

2.2.1.7 Genotoxic Effects

No studies were located regarding the genotoxic effects in humans or animals following inhalation exposure to 1,1,2,2-tetrachloroethane. Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

A group of 1,099 army workers who were exposed to 1,1,2,2-tetrachloroethane vapors in a clothing processing plant showed a very slight increase in the incidence of death due to genital cancers, leukemia, and lymphomas when compared to similar workers whose duties did not involve exposure to 1,1,2,2-tetrachloroethane (Norman et al. 1981). The individuals could have been exposed dermally or by inhalation, but specific exposure levels were not measured. Since the increased incidence was small, no significant excesses were found, and other confounding factors may have been present (i.e., exposure to other chemicals and a lack of occupational histories following exposure), the authors I concluded that the results are difficult to interpret and the observed incidences of cancer may not have been due to 1,1,2,2-tetrachloroethane exposure. This information is inconclusive as to whether 1 ,1,2,2-tetrachloroethane causes cancer in humans.

No other studies were located regarding the carcinogenic effects in animals following inhalation exposure to 1,1,2,2-tetrachloroethane.

2. HEALTH EFFECTS

2.2.2 Oral Exposure

2.2.2.1 Death

A number of human suicides from drinking 1,1,2,2-tetrachloroethane have been reported. The amount consumed varied among individuals, making a minimum lethal dose difficult to determine. Based on the amount found in the stomach, the approximate minimum amounts consumed in these cases were estimated to be 4,100 mg/kg (Hepple 1927), 357 mg/kg (Lilliman 1949), 1,100-9,600 mg/kg (Mant 1953) and an unknown quantity (Elliot 1933; Forbes 1943). The subjects who were poisoned usually lost consciousness within about an hour and died 3-20 hours post ingestion, depending on the amount of food in the stomach. Postmortem examination showed congestion in the lungs in some cases.

The levels that caused death in rats have all been within a narrow range: 319 mg/kg (Smyth et al. 1969), 250 mg/kg (Gohlke et al. 1977), 300 mg/kg/day for 3-4 days (Dow 1988), and 330 mg/kg (Schmidt et al. 1980a). The most complete study (Gohlke et al. 1977) administered the substance by gavage in peanut oil. In a chronic-duration mouse study, a level of 284 mg/kg/day caused death in a majority of exposed mice, after 70 weeks of exposure (NCI 1978).

All reliable LOAEL values from each reliable study for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No studies were located regarding hematological and musculoskeletal effects in humans or animals following oral exposure to 1,1,2,2-tetrachloroethane. The highest NOAEL and all LOAEL values from each reliable study for systemic end points in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. Autopsy reports in humans following suicidal ingestion of at least 1,100 mg/kg of 1,1,2,2-tetrachloroethane revealed congestion and edema in the lungs (Hepple 1927; Mant 1953), but this did not appear to be the primary cause of death. A case of exposure at 9,600 mg/kg was reported to have caused lung collapse (Mant 1953). African men and women

Table 2-2. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Human	once (IN)				4100 M (death)	Hepple 1927
2	Human	once (IN)				357 (death)	Lilliman 1949
3	Human	once (IN)				9600 M (death)	Mant 1953
4	Human	once (IN)				1100 M (death)	Mant 1953
5	Rat (NS)	once (GO)				250 M (LD_{50})	Gohlke et al. 1977
6	Rat (Wistar-C)	once (GO)				330 M (LD_{50})	Schmidt et al. 1980a
7	Rat (Carnworth -Wistar)	once (G)				319 M (LD_{50})	Smyth et al. 1969
	Systemic						
8	Human	once (IN)	Gastro		357 (congestion of stomach lining)		Lilliman 1949
			Hepatic		357 (slight liver congestion)		

Table 2-2. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
9	Human	once (IN)	Resp			9600 M (lung collapse)	Mant 1953
			Gastro		9600M (congestion of esophagus and stomach)		
10	Human	once (IN)	Resp			1100 M (extreme lung congestion and edema)	Mant 1953
			Cardio			1100 M (epicardial and endocardial anoxic petechial hemorrhage)	
			Gastro		1100M (pronounced congestion of gastric mucosa)		
			Hepatic	1100M			
			Renal	1100M			
11	Human	once (IN)	Resp			96 (shallow and rapid respiration)	Sherman 1953
			Cardio			96 (faint pulse)	
12	Human	once (IN)	Resp			100 (shallow breathing)	Ward 1955
			Cardio			100 M (low blood pressure, 60/46)	
13	Rat (Osborne-Mendel)	3-4 d 1x/d (GO)	Hepatic	25M	75M (hyperplasia)		Dow 1988
			Bd Wt	150M	300M (16% depression in final body weight relative to controls)		
14	Rat (Wistar-C)	once (GO)	Hepatic		100M (necrosis and fatty degeneration)		Schmidt et al. 1980a

Table 2-2. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
15	Mouse (B6C3F1)	4 d 1x/d (GO)	Hepatic	25M	75M (centrilobular swelling)		Dow 1988
			Bd Wt	300M			
	Neurological						
16	Human	once (IN)				96 (reversible coma)	Sherman 1953
17	Human	once (IN)				100 (reversible narcosis and absence of corneal and pupillary reflexes)	Ward 1955
18	Rat (Osborne-Mendel)	3-4 d 1x/d (GO)		150M		300 M (CNS depression)	Dow 1988
19	Rat (Wistar)	once (G)		25 F		50 F (blocked avoidance learning)	Wolff 1978
	INTERMEDIATE EXPOSURE						
	Systemic						
20	Rat (Osborne-Mendel)	6 wk 5 d/wk (GO)	Bd Wt	100M		178 M (38% reduction in body weight gain)	NCI 1978
				56[b] F		100 F (24% reduction in body weight gain)	

Table 2-2. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
21	Mouse (B6C3F1)	6 wk 5 d/wk (GO)	Bd Wt	316			NCI 1978
	CHRONIC EXPOSURE						
	Death						
22	Mouse (B6C3F1)	78 wk 5 d/wk (GO)				284 M (33/50 died in week 69-70)	NCI 1978

Table 2-2. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Systemic						
23	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)	Resp		43[c] F, 62 M (labored respiration, wheezing, nasal discharge)		NCI 1978
			Cardio	108 M, 76 F			
			Gastro	108 M, 76 F			
			Hepatic	108 M, 76 F			
			Renal	108 M, 76 F			
			Endocr	108 M, 76 F			
			Dermal	108 M, 76 F			
			Ocular		62 M, 43 F (squinted or reddened eyes with reddish brown discharge)		
			Bd Wt	76 F, 62 M		108 M (20% decrease in body weight gain)	

Table 2-2. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
24	Mouse (B6C3F1)	78 wk 5 d/wk (GO)	Resp	284			NCI 1978
			Cardio	284			
			Gastro	284			
			Hepatic	284			
			Renal	142		284 (tubular nephrosis in males, hydronephrosis in females)	
			Endocr	284			
			Dermal	284			
			Bd Wt	284			
	Reproductive						
25	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)		108 M 76 F			NCI 1978
26	Mouse (B6C3F1)	78 wk 5 d/wk (GO)		284			NCI 1978

Table 2-2. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
	Cancer							
27	Mouse (B6C3F1)	78 wk 5 d/wk (GO)				142	(CEL: hepatocellular carcinoma)	NCI 1978

[a]The number corresponds to entries in Figure 2-2.

[b]Used to derive an intermediate oral MRL of 0.6 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic oral MRL of 0.04 mg/kg/day; dose divided by an uncertainty factor of 1000 (10 for extrapolation from animals to humans, 10 for human variability, and 10 for use of a LOAEL).

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; CNS = central nervous system; d = day(s); Endocr = endocrine; F = female; (G) = gavage; Gastro = gastrointestinal; (GO) = gavage in oil; (IN) = ingestion; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = times

Figure 2-2. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral

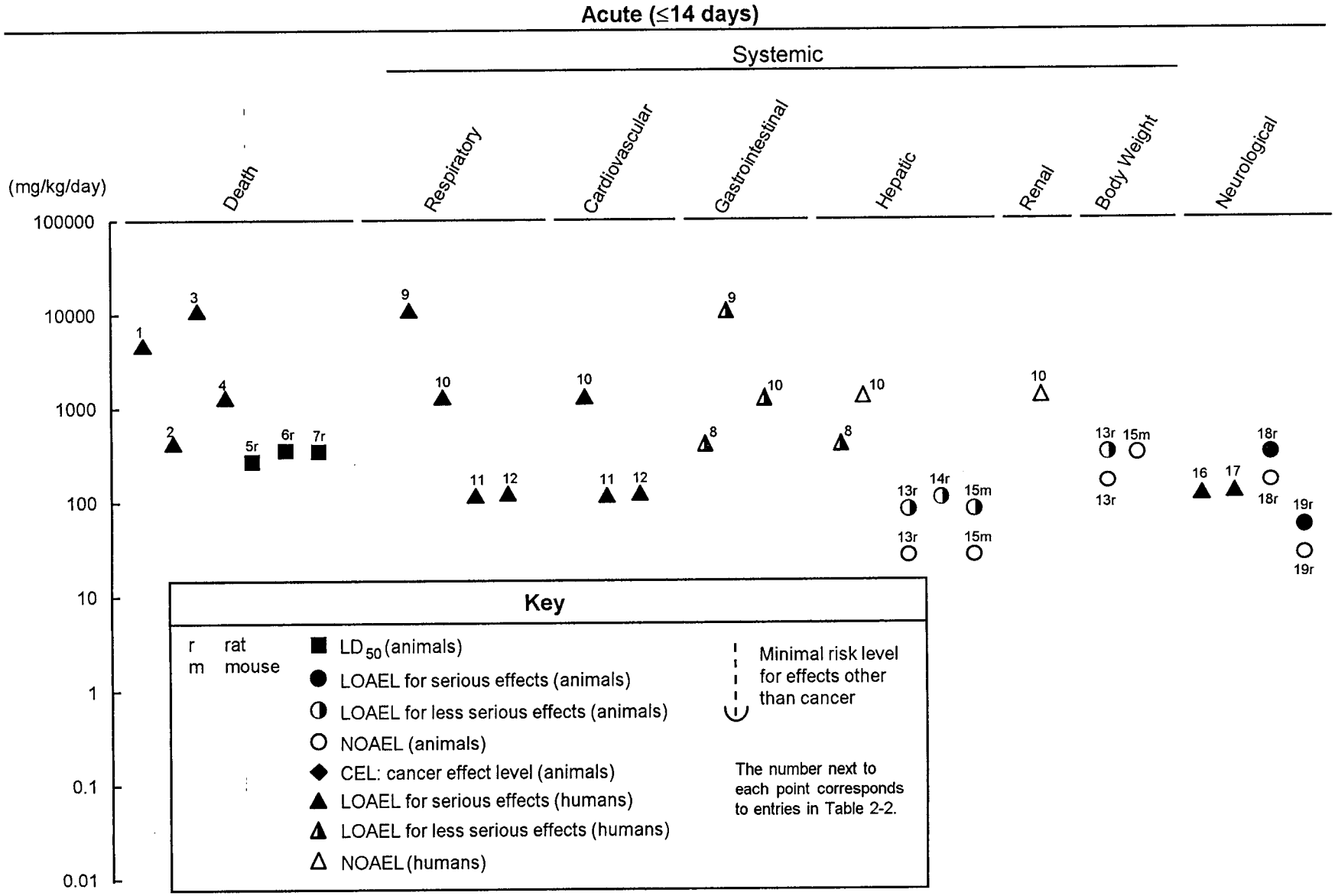


Figure 2-2. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral

Intermediate (15-364 days)

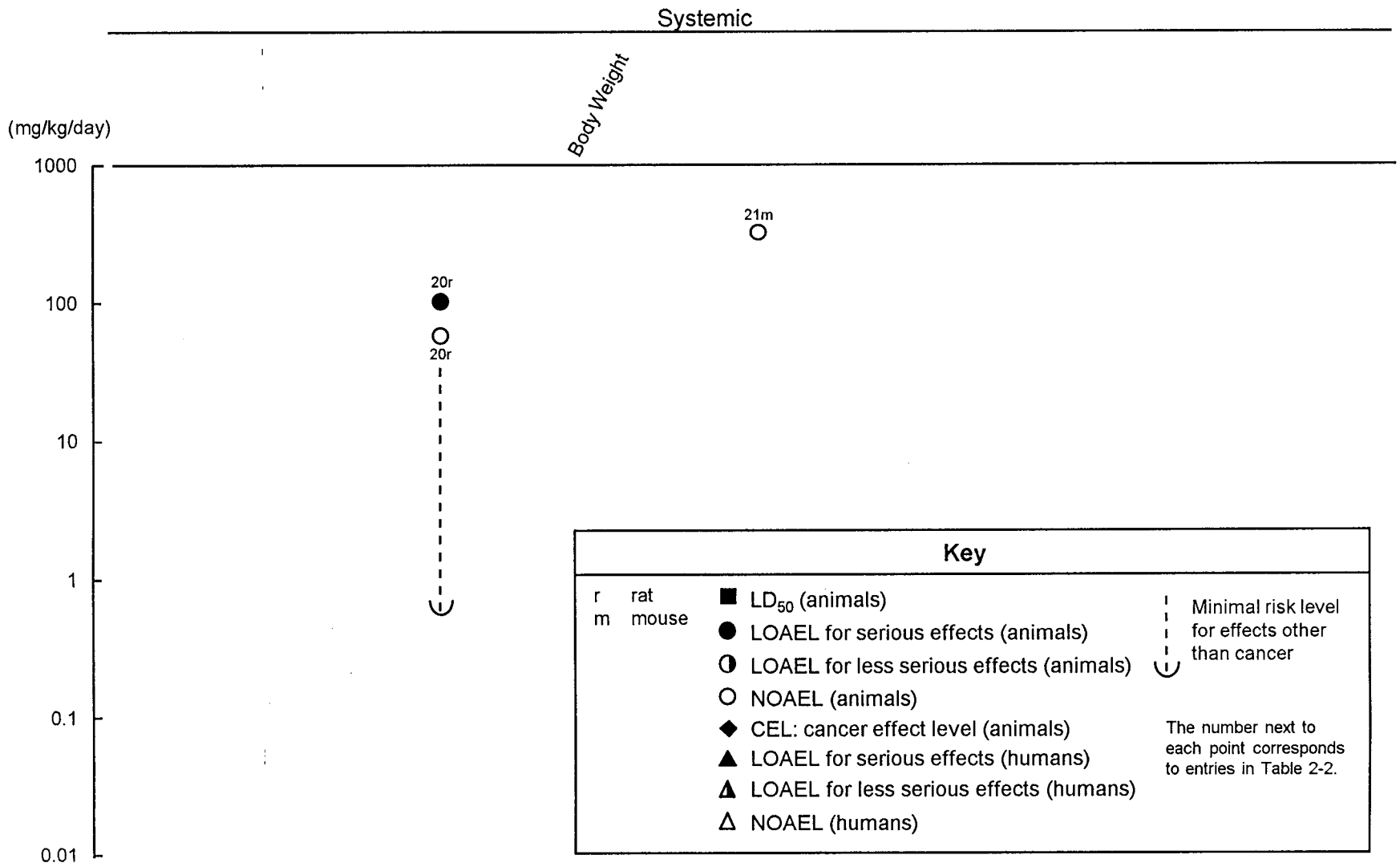
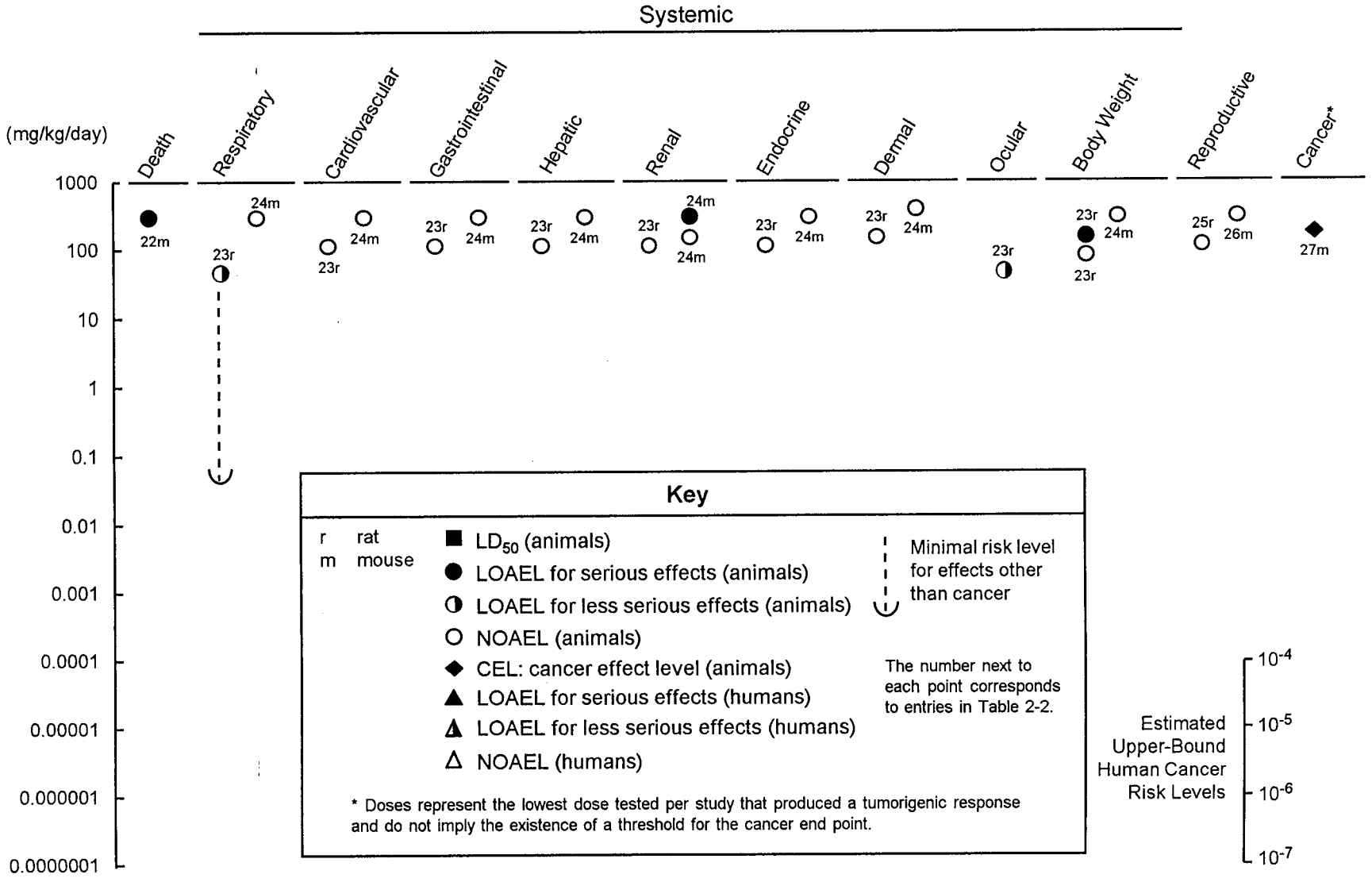


Figure 2-2. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (cont.)

Chronic (≥365 days)



accidentally given oral doses of undiluted 1,1,2,2-tetrachloroethane (approximately 70-l17 mg/kg) experienced shallow breathing during ensuing unconsciousness (Sherman 19.53; Ward 1955).

Rats that received up to 8 mg/kg/day of 1,1,2,2-tetrachloroethane for up to 17 weeks showed no histopathology of the trachea (Gohlke et al. 1977); the lungs were not examined. Longer-term exposure in rats at higher levels (up to 108 mg/kg/day for 78 weeks) produced labored respiration, wheezing, and/or nasal discharge in all groups during the first year and increased as the animals aged. Based on a LOAEL of 43 mg/kg/day for respiratory effects in female rats, a chronic oral MRL was derived as described in the footnote in Table 2-2 and in Appendix A. Mice treated for the same duration at 284 mg/kg/day experienced no respiratory effects (NCI 1978).

Cardiovascular Effects. African men and women accidentally given oral doses (approximately 70-l17 mg/kg undiluted) experienced pronounced lowering of blood pressure (to 60/46) and faint pulse during ensuing unconsciousness (Sherman 1953; Ward 1955). A lethal oral dose (suicide) of 1,100 mg/kg produced epicardial and endocardial anoxic hemorrhage (Mant 1953).

Rats receiving up to 108 mg/kg/day and mice receiving 284 mg/kg/day orally for 78 weeks showed no gross or histological alterations of the heart (NCI 1978).

Gastrointestinal Effects. Single doses of 357 mg/kg or more caused mucosal congestion of the esophagus and upper stomach of humans (Lilliman 1949; Mant 1953). Rats receiving up to 108 mg/kg/day and mice receiving 284 mglkglday oral doses for 78 weeks showed no gross or microscopic histological alterations of the stomach, colon, pancreas or bile duct (NCI 1978).

Hepatic Effects. Autopsy reports showed no evidence of damage to the livers of humans who ingested suicidal doses of 1,1,2,2-tetrachloroethane (Mant 1953). The lack of effect in the liver can be ascribed to the rapid lethality. In another autopsy report, slight congestion of the liver was reported from an accidental poisoning or suicide attempt with 1,1,2,2-tetrachloroethane (Lilliman -1.949).

Rats that received a single oral dose of 100 mg/kg of 1,1,2,2-tetrachloroethane showed unspecified necrosis and fatty degeneration, increased serum leucine aminopeptidase, increased liver ascorbic acid, and increased liver triglyceride levels, but no changes in relative liver weight or body weight (Schmidt et al. 1980a). Centrilobular swelling was observed in mice after a dose of 75 mg/kg/day of

2. HEALTH EFFECTS

1,1,2,2-tetrachloroethane for 4 days (Dow 1988); there were no effects in the livers of rats or mice at a dose of 25 mg/kg/day. At a dose of 300 mg/kg there were increases in mitosis in the mouse hepatocytes. Rats that were gavaged with doses of 3.2 or 8 mg/kg/day of 1,1,2,2-tetrachloroethane for longer periods of time (2 days to 17 weeks) showed minor histological changes in the liver, including inflammation, necrosis, and fatty degeneration (Gohlke et al. 1977).

Renal Effects. Autopsy reports showed no evidence of damage to the kidney of humans who ingested suicidal doses of 1,1,2,2-tetrachloroethane (Mant 1953). The lack of effect can be ascribed to the rapid lethality. No other studies were located regarding renal effects in humans following oral exposure to 1,1,2,2-tetrachloroethane.

Rats treated with 3.2 mg/kg/day of 1,1,2,2-tetrachloroethane for up to 16 weeks showed isolated necrosis of the tubular cortex in the kidney (Gohlke et al. 1977). However, in studies conducted by the NCI (1978), rats treated with up to 108 mg/kg/day for 78 weeks showed no gross or histopathological changes in the kidney. Mice treated for the same duration at 142 mg/kg/day also showed no changes, but at 284 mg/kg/day, male mice died of tubular nephrosis and females experienced hydronephrosis.

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to 1,1,2,2-tetrachloroethane. Rat adrenal and thyroid glands showed changes due to exposure for 120 days to 1,1,2,2-tetrachloroethane. In the thyroid, cell sizes were changed and follicular desquamation was found, and the adrenals showed changes in lipoid content (Gohlke et al. 1977).

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to 1,1,2,2-tetrachloroethane. No changes were noted in the gross appearance of skin or subcutaneous tissues in rats or mice exposed to 1,1,2,2-tetrachloroethane at doses up to 284 mg/kg/day for 78 weeks (NCI 1978).

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to 1,1,2,2-tetrachloroethane. Squinted or reddened eyes with a reddish-brown discharge were noted in male and female rats at all dose levels treated with 1,1,2,2-tetrachloroethane for 78 weeks (NCI 1978

2. HEALTH EFFECTS

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to 1,1,2,2-tetrachloroethane.

In rats treated with 300 mglkglday by gavage for 3-4 days, body weights were depressed by 16% (Dow 1988). No depression in body weight was observed at 150 mg/kg/day. In the 6-week range finding study by NCI (1978), male rats given 178 mg/kg/day by gavage had a 38% reduction in body weight gain, while female rats given 100 mg/kg/day had a 24% reduction. Based on a NOAEL of 56 mg/kg/day for no decreased body weight gain in female rats, an intermediate-duration oral MRL of 0.6 mg/kg/day was derived for 1,1,2,2-tetrachloroethane, as described in the footnote in Table 2-2 and in Appendix A. In contrast, no effects on body weight gain were seen in mice similarly exposed at doses 1316 mg/kg/day. Body weight gain was also depressed in rats, but not mice, treated by gavage with 1,1,2,2-tetrachloroethane for 78 weeks (NCI 1978). Weights of female rats treated with 76 mg/kg/day appeared lower than control weights throughout the treatment; however, by the end of the observation period, no difference was observed compared with the controls. Male rats treated with 108 mg/kg/day, but not 62 mg/kg/day, were 20% lighter than vehicle controls at week 75.

2.2.2.3 Immunological and Lymphoreticular Effects

One investigator reported that the results of an autopsy showed an enlarged and congested spleen in a case of intentional or accidental ingestion of 1,1,2,2-tetrachloroethane (Hepple 1927), while another autopsy study reported that the gross appearance of the spleen was normal (Elliott 1933).

The available animal data on these effects showed that oral administration of 8 mg/kg/day of 1,1,2,2-tetrachloroethane to rats for 16 weeks caused no histopathological changes in the spleen (Gohlke et al. 1977). In the NCI (1978) study, no gross or histological alterations were seen in the spleen or lymph nodes of rats and mice exposed to 1,1,2,2-tetrachloroethane at doses up to 284 mg/kg/day for 78 weeks. Since the histology of the spleen alone is not a good indicator of immune function, and since more specific tests of immune function were not performed;-these doses cannot be considered NOAELs for immunological effects.

2. HEALTH EFFECTS

2.2.2.4 Neurological Effects

By mistake, 3 mL (about 70-l 17 mg/kg) of 1,1,2,2-tetrachloroethane was given orally to several African men and women as a treatment for parasites (Sherman 1953; Ward 1955). The patients lost consciousness within an hour, but were subsequently revived with no apparent after effects. The patients understandably refused further treatment or observation at these clinics.

Rats receiving doses of 300 mg/kg/day for 3-4 day experienced significant central nervous system depression and debilitation (Dow 1988). No more elaborate description of these effects were provided, however. Rats receiving a single 50 mg/kg dose displayed significantly decreased avoidance learning. This effect was not detected at 25 mg/kg (Wolff 1978).

The LOAEL values for each reliable study for neurological effects after acute-duration exposure are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects.

No studies were located regarding reproductive effects in humans following oral exposure to 1,1,2,2-tetrachloroethane.

Reproductive effects were found in rats dosed at 3.2 mg/kg/day, 82 times in 120 days (Gohlke et al. 1977). A high incidence of interstitial edema in the testes, clumped sperm, and epithelial cells in the tubular lumen were observed. Partial necrosis and totally atrophied tubules, giant cells, and two-row germinal epithelial cells with disturbed spermatogenesis were also observed. Some of these changes (unspecified) persisted during the 2-week follow-up observation period. No other reproductive indices were examined. This study had a number of limitations, including an unusual experimental design in which the rats were exposed at a high temperature (35 “C), and uncertainties regarding the language translation. Longer term exposures at higher dose levels, however, produced no gross or- histological alterations in the reproductive organs of male or female rats or mice (NCI 1978). In these studies, male rats were dosed at a level of 108 mg/kg/day for 78 weeks, female rats were dosed at 76 mglkglday for the same period, and mice were dosed at 284 mg/kg/day for the same period. No apparent reason for these discrepancies in effects reported at widely varying doses were found, but the

limitations of the former study complicate its evaluation and make comparison with other studies difficult.

The highest NOAEL and all LOAEL values from all reliable studies for reproductive effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following oral exposure to 1 ,1,2,2-tetrachloroethane.

2.2.2.7 Genotoxic Effects

No studies were located regarding the genotoxic effects in humans or animals following oral administration of 1,1,2,2-tetrachloroethane. Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans following oral exposure to 1,1,2,2-tetrachloroethane.

The initiating and promoting effects of a dose of 99 mg/kg doses to rats was investigated by Story et al. (1986). The study found no initiating action of 1,1,2,2-tetrachloroethane, but a significant promotional effect as indicated by increases in the activity of gamma-glutamyl transpeptidase was reported.

A highly significant dose-related trend in the incidence of hepatocellular carcinomas in both male and female mice has-been reported following oral administration of 142 and 284 mg/kg/day of 1,1,2,2-tetrachloroethane for 78 weeks. The increased incidences were statistically significant at both dose levels compared with controls. No statistically significant increase in the incidence of tumors was found in the treated rats when compared to the controls (NCI 1978). However, rats have been shown to have a low incidence of tumors when treated with carbon tetrachloride, when used as a positive control. This indicated to the NCI that rats may not be sensitive enough to detect tumors

caused by 1,1,2,2-tetrachloroethane. The NCI (1978) concluded that the results in rats provided no evidence of a carcinogenic response in the strain of rats used in this study.

The EPA (IRIS 1994) has calculated an oral slope factor of 0.2 $(mg/kg/day)^{-1}$ for 1,1,2,2-tetrachloroethane, based on the NCI (1978) study showing increased hepatocellular carcinomas in female mice. This ql* corresponds to upper bound individual lifetime cancer risks ranging from $5x10^{-4}$mg/kg/day (10^{-4} risk level) to $5x10^{-7}$ mg/kg/day (10^{-7} risk level). These risk levels are indicated on Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

One human death was reported when a man cleaned up a 1,1,2,2-tetrachloroethane spill with his bare hands (Coyer 1944). He was also exposed to unmeasured levels of 1,1,2,2-tetrachloroethane vapors.

The dermal LD_{50} (lethal dose, 50% kill) for 1,1,2,2-tetrachloroethane in rabbits is 6,360 mg/kg (Smyth et al. 1969) and is recorded in Table 2-3.

2.2.3.2 Systemic Effects

Since humans dermally exposed to 1,1,2,2-tetrachloroethane invariably were reported to have considerable inhalation exposure as well, separation of effects due solely to dermal exposure could not be determined. Those exposed to 1,1,2,2-tetrachloroethane in the workplace showed cardiovascular, gastric, hematological, and hepatic disturbances as noted in the discussion on systemic effects due to inhalation exposure discussed in Section 2.2.1.2 (Coyer 1944; Lobo-Mendonca 1963; Minot and Smith 1921). Total exposure levels and effects due to inhalation versus dermal exposure were not determined in these studies, but air concentrations were reported to vary from 9 to 98 ppm in one study (Lobo-Mendonca 1963).

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, and renal effects in animals after dermal exposure to 1,1,2,2-tetrachloroethane. The LOAEL values for each reliable study for systemic effects in each species and duration category are recorded in Table 2-3.

2. HEALTH EFFECTS

Dermal Effects. Direct application of 514 mg/cm^2 of 1,1,2,2-tetrachloroethane for 16 hours damaged the skin of guinea pigs, causing karyopyknosis and pseudoeosinophilic infiltration (Kronevi et al. 1981). Application of 1,1,2,2-tetrachloroethane (concentration not reported) to the shaved abdomen of rabbits caused hyperemia, edema, and severe blistering (Dow 1944).

Ocular Effects. Humans exposed to 1,1,2,2-tetrachloroethane vapors (130 ppm) for 10 minutes experienced mucosal irritation around the eyes (Lehmann and Schmidt-Kehl 1936). Similarly, guinea pigs exposed to 576 ppm for 5 minutes demonstrated eye closure and squinting; by 15 minutes lacrimation was common (Price et al. 1978). Rats showed these effects at 5,050 ppm. These ocular effects are due to direct contact of the eyes with the vapors rather than a true systemic effect due to inhalation of the vapor. These effects are also described in Section 2.2.1.2 on inhalation effects.

2.2.3.3 Immunological and Lymphoreticular Effects

Data on the immunological and lymphoreticular effects in humans and animals following dermal exposure are limited. One person who died following dermal exposure to 1,1,2,2-tetrachloroethane had an enlarged spleen with nodular areas on its surface (Coyer 1944). This individual cleaned up a spill with his bare hands, and the nature and extent of the exposure were poorly defined.

No studies were located regarding immunological or lymphoreticular effects in animals after dermal exposure to 1,1,2,2-tetrachloroethane.

2.2.3.4 Neurological Effects

Workers in India's bangle industry who dipped their hands into 1,1,2,2-tetrachloroethane and inhaled it had tremors and vertigo in addition to gastric disturbances (Lobo-Mendonca 1963). Specific exposure levels were not measured, but air concentrations were measured at between 9 and 98 ppm. The incidence of tremors was higher among factory workers exposed to higher concentrations,- suggesting a dose-response relationship. Workers in an artificial silk plant experienced fatigue, irritability, headache, and coma (Minot and Smith 1921). Exposure levels were not estimated.

No studies were located regarding neurological effects in animals following dermal application of 1,1,2,2-tetrachloroethane.

Table 2-3. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL			Reference Chemical Form
				Less Serious		Serious	
ACUTE EXPOSURE							
Systemic							
Rat (Sprague-Dawley)	30 min	Ocular	576 ppm	5050 ppm	(lachrimation)		Price et al. 1978
Gn Pig NS	once	Dermal		514 mg/cm^2	(moderate karyopyknosis and cellular infiltration)		Kronevi et al. 1981

Gn pig = Guinea pig; LOAEL = lowest-observable-adverse-effect level; min = minute(s); NOAEL = no-observable-adverse-effect level; NS = not specified

2. HEALTH EFFECTS

No studies were located regarding the following effects in humans or animals following dermal exposure to 1,1,2,2-tetrachloroethane:

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

2.3 TOXICOKINETICS

In both humans and laboratory animals, 1,1,2,2-tetrachloroethane is well absorbed from the respiratory and gastrointestinal tracts, and is absorbed through the skin of animals after dermal exposure. When administered by oral or inhalation routes, 1,1,2,2-tetrachloroethane is extensively metabolized and excreted chiefly as metabolites in the urine and breath. In rats and mice, 1,1,2,2-tetrachloroethane is metabolized to trichloroethanol, trichloroacetic acid, and dichloroacetic acid, which is then broken down to glyoxylic acid, oxalic acid and carbon dioxide; a small percentage of the dose is expired in the breath as the parent compound and as carbon dioxide. In reductive and oxidative metabolism, 1,1,2,2-tetrachloroethane is known to produce reactive radical and acid chloride intermediates, respectively.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

A study in human volunteers was carried out in which a bulb containing ^{38}C1-labelled 1,1,2,2-tetrachloroethane was inserted into their mouths; they immediately inhaled deeply, held their breaths for 20 seconds, and then exhaled through a trap containing granulated charcoal. The excretion of the absorbed compound in the breath and the partition coefficients between blood and air were measured.

2. HEALTH EFFECTS

The study showed that 97% of a single breath of 1,1,2,2-tetrachloroethane is absorbed systemically (Morgan et al. 1970). Two humans were reported to retain approximately 50% of inspired 1,1,2,2-tetrachloroethane, but details on exposure duration and dose were not specified (Lehmann and Schmidt-Kehl 1936).

The total body burden of 1,1,2,2-tetrachloroethane in rats and mice exposed to a vapor concentration 10 ppm for 6 hours was 36 micromole equivalents per kg in rats and 128 micromole equivalents per kg in mice (Dow 1988).

2.3.1.2 Oral Exposure

Studies which quantify absorption following oral exposure in humans were not available. The profound effect of ingestion of large amounts of 1 amounts are absorbed. ,1,2,2-tetrachloroethane indicates that appreciable amounts are absorbed

The total body burden of 1,1,2,2-tetrachloroethane in rats and mice administered 150 mg/kg oral doses of the chemical by gavage in corn oil was about 900 micromole equivalents per kg for both species (approximately 150 mg/kg), indicating that the compound is very well absorbed orally (Dow 1988).

Rats and mice that received 1,1,2,2-tetrachloroethane orally absorbed most of the dose (Milman et al. 1984), but no further details were available on this study. Another study showed that rats and mice given 1,1,2,2-tetrachloroethane via the oral route metabolized approximately 70% of the dose within 48 hours, indicating that at least this much was absorbed (Mitoma et al. 1985).

2.3.1.3 Dermal Exposure

No studies were located regarding absorption following dermal exposure in humans.

Up to 1 mL of 1,1,2,2-tetrachloroethane applied to the skin of mice or guinea pigs was absorbed within a half hour (dose site sealed to prevent evaporation) (Jakobson et al. 1982; Tsuruta 1975).

2. HEALTH EFFECTS

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals following inhalation exposure to 1,1,2,2-tetrachloroethane.

2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans following oral exposure to 1,1,2,2-tetrachloroethane.

A high level of hepatic protein-binding radioactivity was seen in mice administered 1,1,2,2-tetrachloroethane by gavage, followed by a single dose of ^{14}C-1,1,2,2-tetrachloroethane. The amount of 1,1,2,2,-tetrachloroethane-derived radioactivity bound to liver protein was about 2 times that seen in rats (Mitoma et al. 1985). The difference in toxicity of 1,1,2,2-tetrachloroethane in rats and mice may well be due to the higher metabolic rate in mice.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals following dermal exposure to 1,1,2,2-tetrachloroethane.

2.3.3 Metabolism

No studies were located regarding metabolism of 1,1,2,2-tetrachloroethane in humans following inhalation, oral or dermal exposure.

In rats and mice, 60-80% of the administered dose is metabolized and excreted within 48-72 hours following oral doses ranging from 25 to 200 mg/kg (Dow 1988; Mitoma et al. 1985) or an intraperitoneal dose ranging from 210 to 320 mg/kg (Yllner 1971).

1 ,1,2,2-tetrachloroethane is metabolized to trichloroethanol, trichloroacetic acid, and dichloroacetic acid (Ikeda and Ohtsuji 1972; Mitoma et al. 1985). Dichloroacetic acid is then broken down to glyoxylic

acid and formic acid (Yllner 1971). These metabolic pathways are shown in Figure 2-3. Nonenzymatic degradation of 1,1,2,2-tetrachloroethane was thought to occur via dehydrochlorination to form trichloroethylene and tetrachloroethylene in mice (Yllner 1971). More recent data from an in vitro study using rat livers (Koizumi et al. 1982) suggest that the formation of trichloroethylene and tetrachloroethylene from 1,1,2,2-tetrachloroethane may be both enzymatic and non-enzymatic. The above studies relied on calorimetric tests for determination of metabolic products. More definitive studies using gas chromatography and mass spectrometry demonstrated that the hepatic microsomal cytochrome P-450 system in rats catalyzes the conversion of 1,1,2,2-tetrachloroethane to dichloroacetic acid in vitro (Casciola and Ivanetich 1984; Halpert 1982). Those authors indicated that the hydroxylation of 1,1,2,2-tetrachloroethane to form the reactive dichloroacetic acid is the predominant initial metabolic pathway that initiates a series of reactions that leads to the formation of glyoxylic and formic acid.

Eriksson and Brittebo (1991) demonstrated that 1,1,2,2-tetrachloroethane is metabolized in mice by cytochrome P-450 to products that bind to the epithelium of the respiratory and upper alimentary tracts following intravenous administration (3 mg/kg) to mice. The metabolism of 1,1,2,2-tetrachloroethane was increased by chronic ethanol consumption (Sato et al. 1980) and by fasting (Nakajima and Sato 1979) in rats. These treatments did not increase total microsomal cytochrome P-450 content, but are indicative of the involvement of cytochrome P-450 isoenzyme 2El.

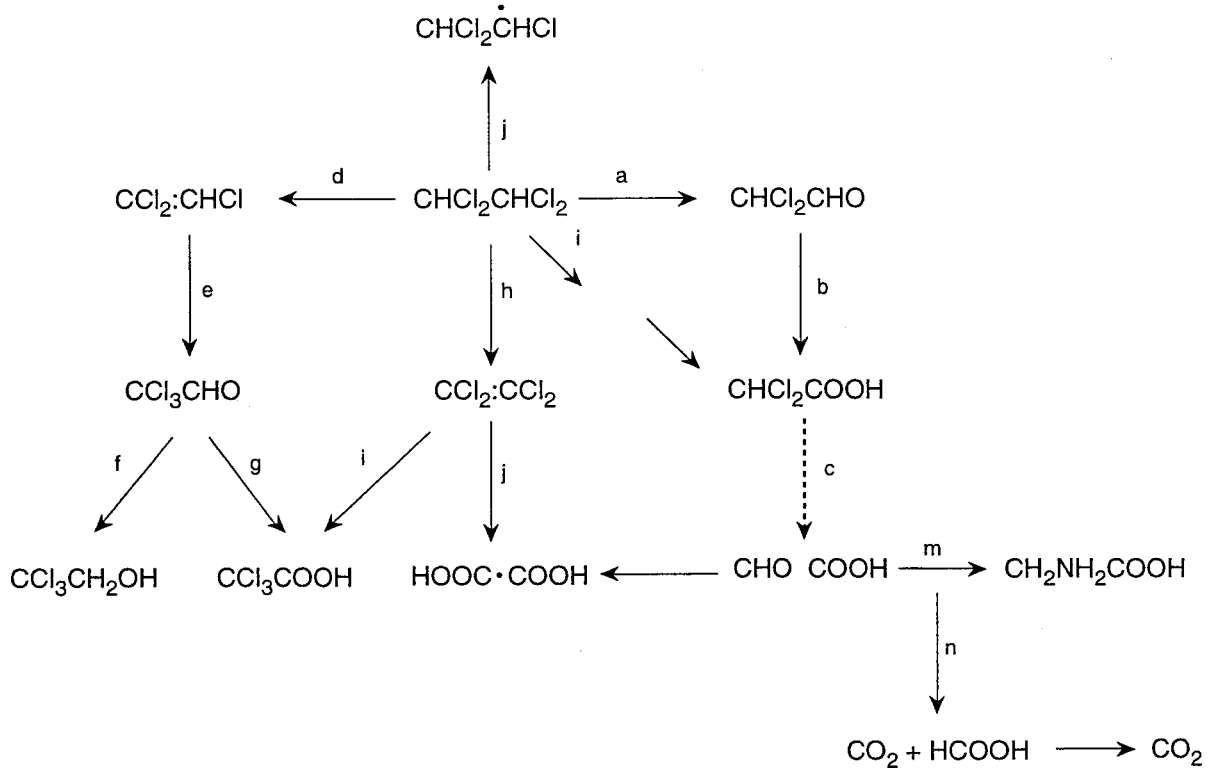
2.3.4 Excretion

2.3.4.1 Inhalation Exposure

A study on human volunteers showed that 3% of inhaled 1,1,2,2-tetrachloroethane was excreted in the breath, and that the urinary excretion rate was 0.015% of the absorbed dose/min (Morgan et al. 1970).

The excretion of-1,1,2,2-tetrachloroethane was tracked for 72 hours following exposure of rats and mice to vapor concentrations of 10 ppm ^{14}C-l,1,2,2-tetrachloroethane for 6 hours (Dow 1988). More than 90% of the absorbed dose was metabolized in both species. The percentage of the recovered radioactivity was reported as follows: in rats, 33% in breath, 19% in urine, and 5% in feces; in mice, 34% in breath, 26% in urine, and 6% in feces.

Figure 2-3. Suggested Metabolic Pathways of 1,1,2,2-Tetrachloroethane



Note: 1,1,2,2-Tetrachloroethane is mainly metabolized (a) by a stagewise hydrolytic cleavage of carbon-chlorine bonds via dichloroacetic acid (b) to glyoxylic acid (c), which is further metabolized (l,m,n). An alternative route (d) is non-enzymic dehydrochlorination to trichloroethylene, which is further metabolized (e,f,g) to trichloroacetic acid + trichloroethanol. Route (h) is oxidation to tetrachloroethylene. Route (i) is the P-450-dependent oxidation, followed by dehydrohalogenation, to form dichloroacetyl chloride. Route (j) is reductive dechlorination.

2. HEALTH EFFECTS

The kinetic constants of 1,1,2,2-tetrachloroethane metabolism in rats exposed to 350 ppm of the chemical for 6 hours were determined in gas uptake studies performed by Gargas and Andersen (1989). The rate of exhalation of 1,1,2,2-tetrachloroethane was measured and, combined with previously published values (Gargas et al. 1989) for partition coefficients for blood/air, liver/blood, muscle/blood, and fat/blood, allowed the successful modeling of the disposition of the chemical in rat. A K_m and V_{max} of 4.77 μm and 12 mg/hr (scaled to a l-kg rat), respectively, were measured.

2.3.4.2 Oral Exposure

No studies were located regarding excretion in humans following oral exposure to 1,1,2,2-tetrachloroethane.

The excretion of 1,1,2,2-tetrachloroethane was followed for 72 hours following oral administration of 1.50 mg/kg doses to rats and mice (Dow 1988). Greater than 90% of the absorbed dose was metabolized in both species. In rats, 41% was excreted in breath, 23% in urine, and 4% in feces. In mice, 51% was excreted in breath, 22% in urine, and 6% in feces.

Mice given an oral dose of 1,1,2,2-tetrachloroethane excreted about 10% of the dose unchanged in the breath. The rest was metabolized and excreted in the breath as CO_2 (10%), in the urine and feces (30%, measured together), and retained in the carcass (27%) after 48 hours. Rats showed similar patterns of excretion (Mitoma et al. 1985). The most comprehensive study of the metabolism and excretion of 1,1,2,2-tetrachloroethane was an intraperitoneal study in mice using ^{14}C-labeled 1,1,2,2-tetrachloroethane. This study showed that after 72 hours, about 4% of the radioactivity was expired unchanged in the breath, 50% was expired as CO_2 ,28% was excreted in the urine, 1% was in the feces, and 16% remained in the carcass (Yllner 1971).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans following dermal exposure to 1,1,2,2-tetrachloroethane.

2. HEALTH EFFECTS

A study describing the elimination of 1,1,2,2-tetrachloroethane in guinea pigs demonstrated that, following dermal absorption, about half of the 1,1,2,2-tetrachloroethane in the blood is eliminated in two hours (Jakobson et al. 1982).

2.4 MECHANISMS OF ACTION

As 1,1,2,2-tetrachloroethane is a volatile, lipophilic molecule of small molecular size, it is well absorbed from both respiratory and gastrointestinal tracts and rapidly distributes throughout tissue compartments by typical passive diffusion processes.

Chlorinated hydrocarbons share similar metabolic fates that involve both oxidative and reductive reactions. These reactions are intimately related to the mechanisms by which halocarbons are activated to proximate toxins. The following mechanisms of activation and toxicity have been investigated for 1,1,2,2-tetrachloroethane.

Toxification Mediated through Oxidation. The presence of the functional group consisting of a terminal dichloromethyl moiety in a molecule, as typified by the drug chloramphenicol, is known to confer toxicity. Chloramphenicol and other dichloromethyl compounds are hydroxylated to form, after spontaneous dehydrohalogenation, reactive acyl chloride intermediates (Halpert 198 1; Halpert et al. 1986) which subsequently bind to crucial proteins to exert their effects. Alternately, these acid chlorides can hydrolyze to form their respective acids. There was clear evidence in the literature reviewed that these pathways were operant for 1 ,I ,2,2-tetrachloroethane. Cytochrome P-450 was found to catalyze the formation of both dichloroacetylated protein adducts (Halpert 1982) and dichloroacetic acid (Halpert 1981). As discussed in Section 2.3.3, these biotransformation reactions were increased by chronic ethanol consumption and fasting, preconditions that are known to induce the levels of cytochrome P-450 isoenzyme IIEl (Johansson et al. 1988; Soucek and Gut 1992). Significantly, a number of low molecular weight volatile halocarbons are metabolized by this isoform, suggesting that it-may be the major contributor to the metabolism of 1,1,2,2-tetrachloroethane as well Guengerich et al. 1991).

Both dichloro- and trichloroacetic acids are known to cause proliferation of peroxisomes (DeAngelo et al. 1986). In the work presented by Dow (1988), this property of the acid metabolites of 1,1,2,2-tetra

chloroethene was noted, and suggested as a possible mechanism by which the halocarbon could elicit hepatotoxic responses.

Toxification Mediated through Reduction. Paolini et al. (1992) investigated the reductive metabolism of 1,1,2,2-tetrachloroethane in mice. Those workers trapped a carbon-centered radical formed in vivo by reductive dehalogenation of 1,1,2,2-tetrachloroethane, a reaction presumably mediated by cytochrome P-450. Additionally, there was evidence of lipid peroxidation. These properties are reminiscent of the metabolism of carbon tetrachloride, where reductive formation of radical products leads to the stimulation of lipid peroxidation and its attendant hepatotoxic effects.

The hepatotoxic and/or carcinogenic effects of 1,1,2,2-tetrachloroethane probably result from the metabolism of that halocarbon by the cytochrome P-450 mixed function oxidase. Mechanisms may involve oxidative and reductive pathways that produce direct- (free radicals and/or acid chlorides) or indirect-acting (di- and trichloroacetic acids) toxins.

2.5 RELEVANCE TO PUBLIC HEALTH

Wide-scale production of 1,1,2,2-tetrachloroethane ceased decades ago. While a few reliable, limited, toxicokinetic and toxicological studies have been done, the majority of the studies available are not recent and do not always meet the standards for current-day data requirements. The chemical is present in hazardous waste sites, but no definitive epidemiological evaluation of the toxicological effects on humans living near such sites has been performed. Instead, only anecdotal reports of humans exposed to very large quantities of 1,1,2,2-tetrachloroethane, either accidentally or by suicide attempts, are available from which to draw conclusions regarding potential effects on humans.

The liver appears to be the target organ most likely to be affected from low-level 1,1,2,2-tetrachloroethane exposure. However, reliable studies which demonstrate the hepatotoxicity of 1,1,2,2-tetrachloroethane toxicity in animals or humans are few in number. 1,1,2,2-Tetrachloroetha is converted by the liver to reactive intermediates, and hepatic hyperplasia and necrosis are most often noted in human and animal exposures. Common to all volatile chlorohydrocarbons, 1,1,2,2-tetrachloroethane causes pronounced depression of the central nervous system, and respiratory depression is a frequent cause of death after acute-duration exposure to high doses.

2. HEALTH EFFECTS

The parent compound is volatile and is readily excreted by exhalation, either as the parent compound or as its metabolite, CO_2 While carbon-atoms derived from the parent may persist in the body, the sparse toxicokinetic data available suggest that this may occur largely from incorporation of those atoms into natural one- and two-carbon pools.

There is limited information available on the effects of 1,1,2,2-tetrachloroethane on reproduction. One report (Gohlke and Schmidt 1972) indicated necrosis and atrophy of the testes, disturbed spermatogenesis, and clumping of the sperm in rats after 120 days of oral exposure to 1,1,2,2-tetrachloroethane. However, there were serious limitations to this study. The NCI (1978) saw no histological changes in the reproductive organs of rats and mice receiving high doses (76-284 mg/kg/day) of the chemical for 78 weeks.

No investigations of developmental effects arising from inhalation, oral, or dermal exposures were available.

Currently, the major probable exposures to humans are those around hazardous waste sites, principally by inhalation exposure and by ingestion of contaminated drinking water. 1,1,2,2-Tetrachloroethane is activated to a proximate toxin by an enzyme system that is induced by prior exposure to ethanol, acetone, and other agents. Persons ingesting significant amounts of ethanol, or exposed to other solvents and chemicals that induce this system may be particularly susceptible to its toxic effects.

Minimum Risk Levels for 1 ,1,2,2-Tetrachloroethane.

Inhalation MRLs

No acute inhalation MRL has been derived for 1 ,1,2,2-tetrachloroethane due to inadequate data. No reliable inhalation studies are available that demonstrate a dose-response from acute exposure to 1,1,2,2-tetrachloroethane.

- An MRL of 0.4 ppm has been derived for intermediate-duration (15-364 days) inhalation exposure to 1,1,2,2-tetrachloroethane.

2. HEALTH EFFECTS

The intermediate-duration inhalation MRL is based on a LOAEL of 130 ppm for minimal hepatic effects in rats, using an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability). In the key study, 55 female Sprague-Dawley rats were exposed to 130 ppm 1,1,2,2-tetrachloroethane for 5 hours per day 5 days per week, for 15 weeks (Truffert et al. 1977). Liver, kidney, adrenal, genital, and lung pathologies were monitored and compared with controls. It was noted that this exposure resulted in increased liver/body weight ratios, and granulation and vacuolization in liver cells. Cellular changes regressed after 19 exposures and were no longer observed following the 39th exposure. Since these hepatic effects were reversible, were consistent with enzyme induction, and did not indicate a preneoplastic effect, they were considered to be "minimal." No significant changes were noted in the other tissues monitored. The major limitation of this study was that only one dose (130 ppm) was examined. However, there were no intermediate-duration inhalation studies with dose-response data that could be used to derive an MRL.

Existing 1,1,2,2-tetrachloroethane data are not considered suitable to derive an MRL for chronicduration inhalation exposure to 1,1,2,2-tetrachloroethane. The one available chronic inhalation study (Gobbato and Bobbio 1968) had variable exposure levels and no controls were used.

Oral MRLs

No acute oral MRL has been derived for 1,1,2,2-tetrachloroethane due to inadequate data. No reliable oral studies are available that demonstrate a dose-response from acute exposure to 1,1,2,2-tetrachloroethane.

- An MRL of 0.6 mg/kg/day has been derived for intermediate-duration (15-364 days) oral exposure to 1,1,2,2-tetrachloroethane.

The intermediate-duration oral MRL is based on a NOAEL value of 56 mg/kg/day for no-decrease in body weight gain in female rats in the 6-week study by NCI (1978). The NOAEL was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). Groups of 5 male and 5 female Osborne-Mendel rats were administered 1,1,2,2-tetrachloroethane by gavage in corn oil 5 days per week for 6 weeks at doses of 56, 100, 178, 316, and 562 mg/kg/day. A 24% reduction in body weight gain was seen at 100 mg/kg/day in the female rats (LOAEL), with no

body weight effects noted at 56 mg/kg/day (NOAEL). In the male rats, a 38% reduction in body weight gain was noted at 178 mgfkglday. No body weight effects were noted in the same study in mice.

- An MRL of 0.04 mg/kg/day has been derived for chronic-duration (>365 days) oral exposure to 1,1,2,2-tetrachloroethane.

The chronic-duration oral MRL is based on a LOAEL value of 43 mg/kg/day for respiratory effects in female rats in the chronic study by NCI (1978). A LOAEL of 43 mg/kg/day was divided by an uncertainty factor of 1,000 (10 for use,of a LOAEL, 10 for extrapolation from animals to humans and 10 for human variability). Groups of 50 male and 50 female Osborne-Mendel rats were administered 1,1,2,2-tetrachloroethane by gavage in corn oil 5 days per week for 78 weeks. Males received doses of 62 or 108 mg/kg/day; females received doses of 43 or 76 mg/kg/day. Body weight gain was monitored, and gross and histological examination of the major organs and tissues was performed. Male rats exhibited labored respiration, wheezing, and nasal discharge at 62 mg/kg/day, while females showed the same symptoms at 43 mg/kg/day. Histological examination revealed no systemic effects in any organs examined, including the lungs and brain. In the same study, groups of mice similarly treated had renal effects at 284 mg/kg/day, consisting of tubular nephrosis leading to death in males and hydronephrosis in females, but not at 142 mg/kg/day. The toxicological significance of the clinical respiratory effects (labored respiration, wheezing, and nasal discharge) is unclear since no histological effects were observed. However, since clinical respiratory effects were also reported in human case reports (Sherman 1953; Ward 1955), these effects appear to be sufficient for the derivation of the MRL. No respiratory effects were found in mice. No other chronic-duration oral studies were located.

Death. Human deaths have occurred following excessive inhalation in the workplace or from dermal exposure from spilling a large amount of the chemical onto one's skin (Coyer 1944; Koelsch 1915; Willcox et al. 1915). 1,1,2,2-Tetrachloroethane has also caused death in humans when amounts more than 3 mL were ingested at one time (Hepple 1927; Mant 1953). Death in animals has also been reported following inhalation, oral, or ,dermal exposure to 1,1,2,2-tetrachloroethane (Dow 1988; Gohlke et al. 1977; NCI 1978; Price et al. 1978; Smyth et al. 1969).

2. HEALTH EFFECTS

Systemic Effects.

Respiratory Effects. When administered by the inhalation or oral route, 1,1,2,2-tetrachloroethane has pronounced effects on the respiratory system, including irritation of the mucous membranes. Respiratory effects in humans have occurred only after exposures to what must have been very high concentrations of 1,1,2,2-tetrachloroethane (Mant 1953; Sherman 1953; Ward 1955). Present-day exposure standards preclude unintentional exposures to these levels of the chemical by humans, but accidental spills are still possible. Rats and guinea pigs experienced labored breathing at high vapor concentrations (Price et al. 1978).

Cardiovascular Effects. The general acute-duration effects of chlorinated hydrocarbons in depression of the central nervous system are manifested by low blood pressure and faint pulse in humans exposed to 1,1,2,2-tetrachloroethane by the inhalation, oral, and dermal routes (Coyer 1944; Mant 1953; Sherman 1953; Ward 1955; Willcox et al. 1915). No studies were located indicating deleterious cardiovascular effects in animals.

Gastrointestinal Effects. Gastrointestinal effects in humans can occur after inhalation or oral exposure. Nausea and vomiting were reported following inhalation exposure (Coyer 1944; Jeney et al. 1957; Lehmann and Schmidt-Kehl 1936; Lobo-Mendonca 1963). In addition to these effects, oral exposure causes irritation of the stomach mucosa and inflammation of the duodenum in humans (Elliot 1933; Forbes 1943; Hepple 1927; Lilliman 1949; Mant 1953).

Hematological Effects. Hematological effects, including reduced hemoglobin content, low white count, anemia, leukocytosis, leukopenia, and decreased hematocrit have been reported following inhalation or dermal exposure to humans (Coyer 1944; Horiguchi et al. 1964; Jeney et al. 1957; Minot and Smith 1921) and inhalation exposure to rats and monkeys (Horiuchi et al. 1962; Schmidt et al. 1972). However, these studies are quite limited due to their age and other factors, and thus the data are inconclusive -as to whether 1,1,2,2-tetrachloroethane will cause hematological effects in humans.

Musculoskeletal Effects. No studies were found on musculoskeletal effects of 1,1,2,2-tetrachloroethane administered by the inhalation, oral, or dermal routes in humans or animals.

2. HEALTH EFFECTS

Hepatic Effects. The liver is an important target organ for 1,1,2,2-tetrachloroethane exposure. In humans, liver effects include jaundice and enlarged liver, and fatty accumulation in the liver (Coyer 1944; Minot and Smith 1921; Parmenter 1921; Willcox et al. 1915). Mice and rats commonly showed signs of hepatic necrosis and fatty degeneration of the liver (Dow 1988; Gohlke and Schmidt 1972; Horiuchi et al. 1962; Schmidt et al. 1980a, 1980b; Willcox et al. 1915). Liver damage has also been noted following intraperitoneal (Takeuchi 1966) and subcutaneous injections in mice (Plaa et al. 1958). The intraperitoneal or subcutaneous routes are only used for laboratory experiments on animals; humans would not be exposed by these routes. Mechanistic studies indicate that mammals can convert 1,1,2,2-tetrachloroethane to reactive metabolic intermediates that may damage the livers of the exposed animals.

Renal Effects. Swollen kidneys and convoluted tubules were observed in some humans acutely exposed orally and by inhalation (Elliot 1933; Hepple 1927; Willcox et al. 1915). Similarly, necrosis of the tubular cortex was reported in one study in rats exposed to oral doses for intermediate periods (Gohlke et al. 1977), and acute-duration inhalation produced interstitial nephritis in rats (Schmidt et al. 1980b). However, NCI (1978) reported no histopathological changes in the kidneys of rats exposed to higher doses of the chemical for 78 weeks, while male mice exposed to the highest dose died of tubular nephrosis and females experienced hydronephrosis. Thus, the data are inconclusive as to whether 1,1,2,2-tetrachloroethane will cause renal effects in humans.

Dermal Effects. In a dermal study, hyperemia and edema of the exposure site was observed in rabbits exposed acutely to undiluted 1,1,2,2-tetrachloroethane (Dow 1944).

Ocular Effects. Humans exposed to 1,1,2,2-tetrachloroethane vapors (130 ppm) for 10 minutes experienced mucosal irritation of the ocular mucosa (Lehmann and Schmidt-Kehl 1936). Similarly, guinea pigs exposed to 576 ppm for 5 minutes demonstrated eye closure and squinting; by 15 minutes, lacrimation was common (Price et al. 1978). Rats showed these effects at 5,050 ppm. These ocular effect are due to-direct contact of the eyes with the vapors rather than a true systemic effect following inhalation of the vapor.

Body Weight Effects. Humans exposed to 1,1,2,2-tetrachloroethane vapors in an occupational setting experienced a 5-15-pound weight loss (Parmenter 1921). However, this weight loss was probably attributable to gastrointestinal disturbances (i.e., nausea, diarrhea, and vomiting) (Parmenter 1921).

2. HEALTH EFFECTS

Several investigators who measured body weight found no effects in animals (Horiuchi et al. 1962; Price et al. 1978; Schmidt et al. 1972, 1980b). Body weight losses after oral exposures not attributable to gastronomic disturbances have been seen in animals after acute-duration or longer exposures (Dow 1988; NCI 1978).

Immunological and Lymphoreticular Effects. There was one report of an enlarged and congested spleen in a case of intentional or accidental ingestion of 1,1,2,2-tetrachloroethane (Hepple 1927). Normal gross appearance of the spleen was reported by another investigator in an exposed patient (Elliott 1933). The limited data available from animal studies are inadequate to determine whether 1,1,2,2-tetrachloroethane will cause immunological effects in humans.

Neurological Effects. Humans exposed to high levels of 1,1,2,2-tetrachloroethane vapors (Lehmann and Schmidt-Kehl 1936) or who have accidentally consumed the chemical (Sherman 1953; Ward 1955) have become dizzy or even unconscious. Inhalation or oral exposure of animals has also resulted in such effects as narcosis, decreased motor activity, ataxia, and inhibition of learning (Dow 1988; Horvath and Frantik 1973; Pantelitsch 1933; Price et al. 1978; Wolff 1978). These studies indicate that 1,1,2,2-tetrachloroethane affects the central nervous system. However, the effects on the nervous system that have been described are general and non-specific.

Reproductive Effects. No studies were located regarding reproductive effects in humans following exposure to 1,1,2,2-tetrachloroethane. No effects were seen on the histology of the reproductive organs in female rats exposed by inhalation to 1,1,2,2-tetrachloroethane for 15 weeks (Truffert et al. 1977). Rats exposed orally to 1,1,2,2-tetrachloroethane were reported to have irreversible histological changes in the testes; however, this study has severe limitations and these changes were not observed in other studies (Gohlke et al. 1977). The effects that 1,1,2,2-tetrachloroethane might have on the reproductive capacity of humans are not known.

Developmental Effects. No studies were found on the developmental effects of 1,1;2,2-tetrachloroethane administered by the inhalation, oral, or dermal routes in humans. However, offspring of male rats exposed to 2 ppm 1,1,2,2-tetrachloroethane 4 hours per day during a 9-month period showed no gross malformations. There was no effect on the number of offspring per litter, neonatal body weight, viability of the offspring, or sex ratios on day 84 (Schmidt et al. 1972). In a study on the developmental effects of intraperitoneally administered 1,1,2,2-tetrachloroethane during gestation in

mice (Schmidt 1976), the chemical was found to have no effects at 300 mg/kg, while an increase in post-implantation losses was seen at 400 and 700 mg/kg. At 700 mg/kg, moderate effects on skeletal development were also seen, but no effects on fetal weight, number of resorptions, or number of pregnancies were observed. The authors considered 1,1,2,2-tetrachloroethane to be embryotoxic, but only weakly teratogenic, when given to animals via the intraperitoneal route. These studies provide little information on what developmental effects might occur in humans who are exposed to 1,1,2,2-tetrachloroethane in the air, water, or soil.

Genotoxic Effects. No studies were located regarding genotoxic effects in humans or animals following inhalation, oral, or dermal exposure to 1,1,2,2-tetrachloroethane.

In in ***vitro*** tests of genotoxicity, 1,1,2,2-tetrachloroethane has shown mixed results in assays for gene mutation, chromosomal aberration, DNA repair and synthesis, and cell transformation (see Table 2-4).

No studies were found that actually tested 1,1,2,2-tetrachloroethane for genotoxic effects in intact mature animals or humans, which would be more reliable predictors of human effects than in vitro experiments. Of the tests that used mammalian cells as indicators, the majority were negative. Of those using bacteria, yeast, or insects, about half yielded negative results. The probability that 1,1,2,2-tetrachloroethane may be genotoxic in mammalian cells is low, but existing evidence is insufficient to predict whether the chemical may pose a genotoxic threat to humans.

Cancer. It is questionable whether 1,1,2,2-tetrachloroethane will cause cancer in humans. An epidemiological study on the relationship between exposure to 1,1,2,2-tetrachloroethane and subsequent development of tumors in humans (Norman et al. 1981) showed a weak correlation between exposure to 1,1,2,2-tetrachloroethane and development of genital tumors and leukemia. However, the authors believed that other uncontrolled factors may have affected the results, so that no definite conclusions could be drawn from the study.

The ability of 1,1,2,2-tetrachloroethane to induce cancer in animals was tested in two bioassays. A study by the NCI (1978) looked for tumors in B6C3F_1 mice and Osborne-Mendel rats following oral administration of 1,1,2,2-tetrachloroethane for 78 weeks, followed by 32 weeks of observation. A second study focused on the development of pulmonary tumors in Strain A mice following intraperitoneal administration of 80-400 mg/kg/day of 1,1,2,2-tetrachloroethane for 2-6 weeks (Theiss

Table 2-4. Genotoxicity of 1,1,2,2- Tetrachloroethane *In Vitro*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Yeast	Gene mutation	NT	+	Callen et al. 1980
Salmonella typhimurium	Gene mutation	–	–	Mitoma et al. 1984
		–	–	Nestman et al. 1980
		NT	+	Brem et al. 19074
Drosophilia	Gene mutation	NT	+	Woodruff et al. 1985; McGregor 1980
Chinese hamster ovary cells	Chromosomal aberrations	–	–	Galloway et al. 1987
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Galloway et al. 1987
BALB/c 3T3 mouse cells	Cell transformation	NT	–	Little 1983; Tu et al. 1985
E. coli	DNA growth, repair or synthesis	NT	+	Rosenkrantz 1977; Brem et al. 1974
Rat hepatocytes		NT	–	Williams 1983
Mouse hepatocytes		NT	–	Williams 1983
Human embryonic intestinal cells		–	NT	McGregor 1980

NT = not tested; – = negative results; + = positive results.

et al. 1977). A highly significant increase in the incidence of hepatocellular carcinomas in mice in the NCI study was reported, while the rats had no significant increase in tumors at either site. However, an increased incidence of hepatocellular carcinomas in $B6C3F_1$ mice is not an unusual situation (Haseman 1984). Many chemicals increase the spontaneous rate of hepatocellular carcinomas in these mice, but do not produce tumors in other sites in mice or in rats. A marginally significant increase in pulmonary tumors in mice was reported at 400 mg/kg/day, but not at lower doses (Theiss et al. 1977).

Since the evidence for carcinogenicity in animals is restricted to one species, and the information from humans is inconclusive, 1,1,2,2-tetrachloroethane has been classified in Group C, as a "possible human carcinogen" by the EPA (IRIS 1994) and as Group 3 "not classifiable as to carcinogenicity in humans" by IARC (1987).

There is some information on a mechanism by which 1,1,2,2-tetrachloroethane may cause liver tumors in animals. 1,1,2,2-Tetrachloroethane was examined in a rat liver foci assay for its initiating and promoting potential for tumor production in male rats (Story et al. 1986). 1,1,2,2-Tetrachloroethane had no effects in the initiation protocol. The authors suggest that this lends support to the-hypothesis that 1,1,2,2-tetrachloroethane induces liver tumors primarily through a promoting mechanism.

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several

different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 1,1,2,2-tetrachloroethane are discussed in Section 2.6.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1,1,2,2-tetrachloroethane are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to 1,1,2,2-Tetrachloroethane

There currently are no specific biomarkers available to quantify exposure to 1,1,2,2-tetrachloroethane. However, metabolites of 1,1,2,2-tetrachloroethane, including trichloroacetic acid, trichloroethanol, and trichloroethanol glucuronide, may be measured in blood and urine (Breimer et al. 1974; Christensen et al. 1988; Koppen et al. 1988) (see Chapter 6). However, these metabolites are common to several types of chlorinated ethanes and would not be specifically indicative of exposure to 1,1,2,2-tetrachloroethane. Also, 1,1,2,2-tetrachloroethane is metabolized and excreted rather quickly, and the test might only indicate whether the person had been exposed within the last few days. If such a test of metabolite levels were available, the levels in the human body might be used to determine if adverse health symptoms were specifically the result of 1,1,2,2-tetrachloroethane exposure.

2. HEALTH EFFECTS

2.6.2 Biomarkers Used to Characterize Effects Caused by 1,1,2,2-Tetrachloroethane

There currently are no biomarkers available to characterize effects caused by 1,1,2,2-tetrachloroethane. However, since 1,1,2,2-tetrachloroethane has the potential to cause liver damage at very high doses, it may be possible to correlate changes in urinary metabolites with serum indicators of liver malfunction, although the metabolites would not be specific for 1,1,2,2-tetrachloroethane.

2.7 INTERACTIONS WITH OTHER CHEMICALS

In efforts to find treatments for acute-duration 1,1,2,2-tetrachloroethane poisoning, various substances have been tested to determine if they altered the toxicity of 1,1,2,2-tetrachloroethane in rats (Laass 1973a, 1973b, 1974a, 1974b). The survival times were increased when 1,1,2,2-tetrachloroethane was administered with castor oil, but decreased when administered orally with milk. Survival time was also decreased when 1,1,2,2-tetrachloroethane was given with mineral oil or with paraffin.

Alcohol, an inducer of cytochrome P-450 form IIEl, increased the metabolism (Sat0 et al. 1980) of 1,1,2,2-tetrachloroethane and intensified the effects of 1,1,2,2-tetrachloroethane in rats (Gohlke and Schmidt 1972). This indicates that humans who consume alcohol may be at increased risk for toxic effects from 1,1,2,2-tetrachloroethane. This is also the case for several other chlorinated aliphatic hydrocarbons. However, although alcohol combined with 1,1,2,2-tetrachloroethane increased the relative weight of the testes in rats (Schmidt et al. 1972), it did not alter the effects of 1,1,2,2-tetrachloroethane on the histopathology or function in the liver, nor was there damage to the kidneys, spleen, adrenals, brain, or thyroid.

Acetone pretreatment did not increase the severity of liver injury in rats given 1,1,2,2-tetrachloroethane. Additionally, rats given 1,1,2,2-tetrachloroethane in addition to 1,1-dichloroethylene or tetrachloroethylene exhibited a decrease in hepatotoxicity from animals given 1,1-dichloroethylene or tetrachloroethylene alone (Charbonneau et al. 1991).

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,1,2,2-tetrachloroethane than will most persons exposed to the same level of 1,1,2,2-tetrachloroethane in the environment. Reasons

include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting endproduct metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

While no populations with unusual susceptibility to the health effects of 1,1,2,2-tetrachloroethane could be identified based on the available literature, the literature reviewed indicated that factors that increase the levels of the toxicating enzyme may be predicted to increase individual susceptibility. Those factors include chronic alcohol consumption, diabetes, and fasting (Soucek and Gut 1992).

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of 1,1,2,2-tetrachloroethane. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 1,1,2,2-tetrachloroethane. When specific exposures have occurred, poison control centers, and medical toxicologists should be consulted for medical advice.

2.9.1 Reducing Peak Absorption Following Exposure

Human exposure to 1,1,2,2-tetrachloroethane may occur by inhalation, ingestion, or dermal contact. Concentrated vapors are irritating to the eyes and upper respiratory tract, and once absorbed can cause central nervous system and respiratory depression. Unprotected skin exposure can cause-defatting and subsequent dermatitis. Suggested treatment for exposed individuals includes moving them to fresh air and administering 100% humidified supplemental oxygen. The potential risk of rapid central nervous system and respiratory depression usually outweighs the potential risk (e.g., aspiration of vomitus) of administering syrup of ipecac to induce emesis (TOMES 1993). Once in the care of a health

professional, gastric lavage is suggested if it can be performed within minutes of the exposure to reduce the amount of absorbed solvent.

Following acute high-level exposure to some chlorinated solvents by any route, hypotension and cardiac arrhythmias due to myocardial sensitization to catecholamines have led to ventricular fibrillation and death (TOMES 1993). There is no specific treatment for 1,1,2,2-tetrachloroethane exposure except for supportive measures to combat the effects of central nervous system and respiratory depression, and cardiac arrhythmias.

2.9.2 Reducing Body Burden

The body does not retain significant amounts of 1,1,2,2-tetrachloroethane. Currently, there is no recognized treatment to enhance elimination. The orthodox treatment for ingestion is entirely supportive. One potential method for enhancing elimination, however, is to increase the ventilation rate, thereby enhancing elimination via the lung. In a 6-year-old boy who had ingested 12-16 g of tetrachloroethylene, controlled hyperventilation over a 5-day period enhanced pulmonary excretion of the chemical (Koppel et al. 1985). This technique may be applicable to other volatile solvents like 1,1,2,2-tetrachloroethane.

Stimulation of the metabolism of 1,1,2,2-tetrachloroethane may also lead to enhanced elimination, but it can also result in formation of larger amounts of toxic metabolites. Thus, the risks of this approach may outweigh the benefits.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

Clinical effects caused by acute 1,1,2,2-tetrachloroethane exposure include central nervous system depression, nephritis, and toxic hepatitis (HSDB 1994). Other effects include malaise, dizziness, fatigue, headache, and lightheadedness, all of which may disappear rapidly after the exposure ceases. The mechanism-of action for the central nervous system effects has not been clearly established, but it is probable that it is related to solvent effects on neuronal membranes exerted by many halogenated aliphatic hydrocarbons.

2. HEALTH EFFECTS

Ethanol in alcoholic beverages may compete with or enhance the metabolic activation of solvents and could possibly increase the severity of health effects, particularly liver toxicity. Alcoholic beverages should be avoided by persons exposed to 1,1,2,2-tetrachloroethane and other solvents of this nature.

Mechanisms have been proposed for the hepatotoxic action of this halocarbon (Dow 1988; Halpert 1981; Halpert et al. 1986). These include generation of reactive free radicals and acid chlorides. Dietary antioxidants may modulate the toxicity caused by the former, but no established treatments are available for the latter. It is concluded that avoiding co-exposures to substances that enhance the activation of 1,1,2,2-tetrachloroethane (e.g., acetone and ethanol) provide the best means of interfering with the toxification of the absorbed chemical.

2.10 ADEQUACY OF THE DATABASE

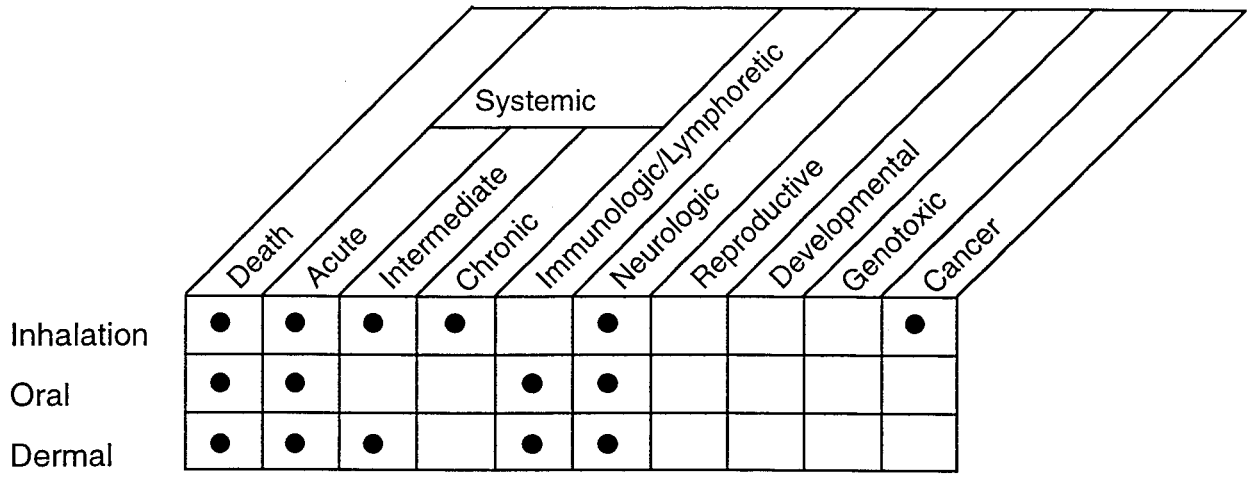
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,1,2,2-tetrachloroethane is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,1,2,2 tetrachloroethane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

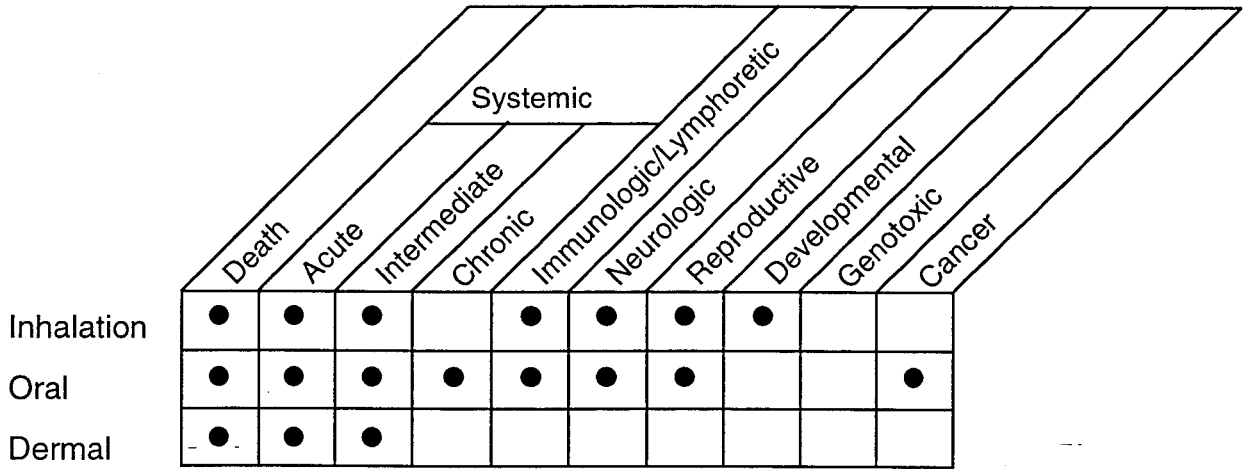
2.10.1 Existing Information on Health Effects of 1 ,I ,2,2-Tetrachloroethane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1,2,2-tetrachloroethane are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,1,2,2-tetrachloroethane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing

Figure 2-4. Existing Information on Health Effects of 1,1,2,2-Tetrachloroethane



Human



Animal

● Existing Studies

information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As seen in Figures 2-4, data exist for inhalation exposure of humans for death, systemic effects of acute-, intermediate-, and chronic-duration exposure, neurological effects, and cancer. A few human deaths have been reported following excessive inhalation exposure to 1,1,2,2-tetrachloroethane in occupational settings. Effects reported in humans exposed in the workplace consist of gastric distress including pain, nausea, vomiting, loss of appetite, and loss of body weight; increases in the number of white blood cells; jaundice, enlarged liver, liver degeneration, and cirrhosis; neurological symptoms such as headache, tremors, dizziness, numbness, and drowsiness; and possibly genital cancer and leukemia or lymphoma. In one experimental inhalation study, male volunteers experienced mucosal irritation, nausea, vomiting, and dizziness upon exposure to high levels of 1,1,2,2-tetrachloroethane. Data for oral exposure of humans consist mainly of case reports of suicidal or accidental ingestion of 1,1,2,2-tetrachloroethane, with data for death, systemic effects of acute-duration exposure, immunological/lymphoreticular and neurological effects. Autopsy findings in suicide cases included congestion and edema in the lungs and lung collapse, mucosal congestion of the esophagus and upper stomach, and epicardial and endocardial anoxic hemorrhage. In cases of humans accidentally given oral doses of 1,1,2,2-tetrachloroethane for parasite treatment, effects consisted of shallow breathing, pronounced lowering of blood pressure, and faint pulse during ensuing unconsciousness. One death was reported when a man cleaned up a 1,1,2,2-tetrachloroethane spill with his bare hands. Workers in India's bangle industry who dipped their hands in 1,1,2,2-tetrachloroethane, as well as inhaled it, had tremors, headache, and dizziness in addition to gastric disturbances. Mucosal irritation of the eyes has also been observed in humans exposed to 1,1,2,2-tetrachloroethane in air by direct contact of the concentrated vapor with the eyes.

For animals exposed by inhalation, data exist for death; systemic effects of acute- and intermediateduration; and immunological/lymphoreticular, neurological, reproductive, and developmental effects. Systemic effects consisted of labored respiration, hematological effects, and hepatic effects. Immunological effects consisted of a decrease in titer and an increase in the electrophoretic mobility of specific antibodies to typhoid in rabbits. Neurological effects included decreased motor activity, loss

of reflexes, ataxia, prostration, and narcosis. No reproductive or developmental toxicity was associated with inhalation exposure of animals. Data for oral exposure of animals exist for death; systemic effects of acute-, intermediate-, and chronic-duration exposure; immunological/lymphoreticular, neurological, and reproductive effects; and cancer. Systemic effects consisted of hepatic, thyroid, and adrenal effects, and decreases in body weight gain. Information on immunological/lymphoreticular effects is limited to histopathological effects on the spleen. Neurological effects consisted of central nervous system depression, debilitation, and decreased avoidance learning. An oral study in rats indicated an effect on spermatogenesis; however, the interpretation of the study was confounded by the fact that the rats had been maintained at a high temperature (35 °C). Cancer data consist of a significantly increased incidence of hepatocellular carcinoma in mice exposed orally. Existing data in animals exposed dermally to 1,1,2,2-tetrachloroethane are limited to an LD_{50} in rabbits; karyopyknosis and pseudoeosinophilic infiltration in guinea pigs; and eye closure, squinting, and lacrimation in guinea pigs and rats acutely exposed to the vapors.

2.10.2 Identification of Data Needs

Acute-Duration Exposure. Several studies are available regarding the effects of acute-duration exposures to 1,1,2,2-tetrachloroethane, both in humans (Coyer 1944; Hepple 1927; Lehmann and Schmidt-Kehl 1936; Sherman 1953; Ward 1955) and animals (Deguchi 1972; Dow 1988; Horiuchi et al. 1962; Price et al. 1978). These studies have identified the liver, central nervous system, and respiratory system as the major organ systems affected in both humans and animals following inhalation and oral exposure. However, the data were deemed insufficient to derive acute-duration inhalation or oral MRLs, since most of these studies are dated and are not designed with the same degree of scientific rigor as more recent studies. Well designed, recent studies are needed on acuteduration inhalation and oral exposure to 1,1,2,2-tetrachloroethane. Data for dermal exposure routes are limited, but this is not a primary route of human exposure for persons living near hazardous waste sites where 1,1,2,2-tetrachloroethane may be found.

Intermediate-Duration Exposure. Reports of intermediate-duration exposures to humans by the oral and inhalation routes have been somewhat anecdotal and dated, and their interpretations complicated by uncertainties in levels of exposure to 1,1,2,2-tetrachloroethane and other chemicals (Jeney et al. 1957; Koelsch 1915; Lobo-Mendonca 1963; Minot and Smith 1921; Parmenter 1921; Willcox 1915). Though mostly qualitative, these studies have confirmed that the same organ systems

are affected as those for acute-duration exposure. Controlled animal studies using the oral and inhalation routes and several concentrations of 1,1,2,2-tetrachloroethane support the findings of the human studies (Dow 1944; Gohlke et al. 1977; Horiuchi et al. 1962; NCI 1978; Schmidt et al. 1972, 1975; Truffert et al. 1977). Only limited intermediate-duration dermal exposures were studied in humans (Minot and Smith 1921) and rabbits (Dow 1944), but this is not a primary route of current human exposure. Inhalation exposure data are sufficient to derive an MRL of 0.4 ppm based on liver effects in rats (Truffert et al. 1977). However, only one dose was tested in this study; thus, well designed intermediate inhalation studies using several doses are needed to better understand the toxicity of 1,1,2,2-tetrachloroethane via inhalation exposure. An intermediate oral MRL of 0.6 mg/kg/day was calculated from a NOAEL based on body weight effects data in female rats (NCI 1978).

Chronic-Duration Exposure and Cancer. Limited data are available on effects of chronicduration exposure for the inhalation route in humans and animals. Insufficient inhalation data are available to derive a chronic inhalation MRL. The systemic effects of long-term repetitive oral exposure of mice and rats to 1,1,2,2-tetrachloroethane have been studied via gavage using several dose levels (NCI 1978). Contrary to shorter-duration experiments by other researchers, significant effects in the NCI studies were limited to the kidney in mice. Reexamination of these findings would help resolve this discrepancy. From this study, a chronic oral MRL of 0.04 mg/kg/day was calculated from a NOAEL based on respiratory effects in female mice (NCI 1978). Additional studies by more relevant routes of exposure, such as drinking water or feed, would be helpful to better define the toxicity of 1,1,2,2-tetrachloroethane via oral exposure.

There is one study on the possible carcinogenic effect of 1,1,2,2-tetrachloroethane on humans via inhalation exposure (Norman et al. 1981), and there are several oral studies of the effects on animals (NCI 1978; Theiss et al. 1977). The human study was inconclusive and in the NCI (1978) study, liver tumors were found in mice after long-term oral exposure. However, this species has a high rate of spontaneous incidence of these tumors, and this data may not be indicative of carcinogenic risk in humans. Theiss et al. (1977) injected 1,1,2,2-tetrachloroethane in mice, and found no increase in the number of lung tumors in mice receiving the low- and mid-level doses of 1,1,2,2-tetrachloroethane, while a marginally significant increase in lung tumors was seen in the high-dose group.

2. HEALTH EFFECTS

Since humans are most likely to be exposed via the inhalation or oral routes, long-term animal studies using these routes would be useful. Studies that use a range of doses in several species and are able to identify a threshold for the non-cancer effects of this chemical would also be useful. There are no studies of the effect of chronic-duration dermal administration of 1,1,2,2-tetrachloroethane in humans or animals. Determination of the effect of chronic-duration dermal administration of 1,1,2,2-tetrachloroethane to animals would be methodologically problematic due to inadvertent oral and or inhalation exposures. Additionally, chronic-duration dermal exposure is unlikely for humans. Therefore, chronic-duration studies by this route are not recommended.

Genotoxicity. Information on the in vivo genotoxic effects of 1,1,2,2-tetrachloroethane is lacking for both humans and animals, although there are a number of *in vitro* tests of the mutagenicity of 1,1,2,2-tetrachloroethane (see Table 2-4). This type of data is not sufficient to determine if 1,1,2,2-tetrachloroethane is genotoxic in humans. *In vivo* testing and *in vitro* testing on human cell lines would help determine if 1,1,2,2-tetrachloroethane is genotoxic in humans. The known metabolism of 1,1,2,2-tetrachloroethane to reactive acid chlorides and/or free radical products suggests that genotoxic effects in humans and other mammals are possible.

Reproductive Toxicity. There were no human reproductive toxicity studies reported for 1 ,1,2,2-tetrachloroethane. Production of 1,1,2,2-tetrachloroethane has nearly ceased in this country, and it will probably not be possible to study reproductive effects associated with occupational exposure to this chemical. The effects of oral and inhalation exposures of various durations have been studied in animals. Atrophy of the seminal tubules was found after acute-duration inhalation (Schmidt et al. 1972) and after intermediate-duration ingestion in rats (Gohlke et al. 1977). However, conflicting data was provided by other workers. After acute-duration inhalation at 6,310 ppm, no effects on the testes, epididymes, ovaries, or uteruses were found in rats (Price et al. 1978). Similarly, an intermediateduration study by inhalation (Horiuchi et al. 1962) reported no effects on the testes in one monkey. Additionally, chronic-duration oral administration of 1,1,2,2-tetrachloroethane to rats and mice caused no increase in histological alterations in reproductive organs (NCI 1978). These conflicting results should be resolved by studies in animals using modern techniques and protocols for measuring adverse effects on reproductive parameters for both males and females.

Developmental Toxicity. There is only one study on the effects of inhalation or oral administration of 1,1,2,2-tetrachloroethane on development in humans or animals. In this intermediate-

duration inhalation study, male rats were exposed to 1 ,I ,2,2-tetrachloroethane and mated with unexposed females, and the F_1 generation was observed for 12 weeks. No effects on the number of offspring per litter, neonatal body weight, offspring viability, or sex ratios were observed. No gross malformations in offspring were detected (Schmidt et al. 1972). Another animal study (Schmidt 1976) indicates that intraperitoneal injections of 1,1,2,2-tetrachloroethane into pregnant mice cause fetal abnormalities and resorptions. Well conducted animal studies, particularly by the inhalation and oral routes, are needed to determine the potential embryotoxicity, fetotoxicity, and teratogenicity of 1,1,2,2-tetrachloroethane.

Immunotoxicity. There is a lack of useful information on the effects of 1,1,2,2-tetrachloroethane on the immune system in humans, and the information available from animal studies in this area is very limited. The human studies were dated, lacked information on the dose received and duration of exposure, and reported only gross effects on the appearance of the spleen (Coyer 1944; Elliot 1933; Hepple 1927). Similarly, only superficial information on the effect of 1,1,2,2-tetrachloroethane on the spleen was provided in studies conducted in the rat (Gohlke et al. 1977; Schmidt et al. 1975) and monkey (Horiuchi et al. 1962). Since immunological end points are known to be very sensitive indicators of the toxicity of many chemicals, a battery of immunological function tests in animals would be helpful in clarifying whether 1,1,2,2-tetrachloroethane is an immunotoxicant.

There are no data on sensitization as a result of exposure to 1,1,2,2-tetrachloroethane by any route in humans or animals. Dermal sensitization tests in animals may be useful, because of potential dermal exposure of humans to soil and water near hazardous waste sites.

Neurotoxicity. 1,1,2,2-Tetrachloroethane is known to have neurological effects on humans and animals exposed by the dermal, oral, and inhalation routes. The effects are related to generalized central nervous system depression and are similar across species and routes of administration. These include hyperactivity and excitability, giving way to narcosis, coma, ataxia, and prostration. These effects in humans are found after acute-duration inhalation (Lehmann and Schmidt-Kehlt936), intermediate-duration inhalation (Hamilton 1917; Horiguchi et al. 1964; Jeney et al. 1957), acute-duration oral administration (Sherman 1953; Ward 1955), and intermediate-duration dermal exposures (Lobo-Mendonca 1963; Minot and Smith 1921). For the most part, however, there was a lack of precise data on dose levels. Concomitant exposures to other solvents may have occurred. These effects were found in the rat (Gohke and Schmidt 1972; Horvath and Frantik 1973; Price et al. 1978;

Schmidt et al. 1975; Truffert et al. 1977), mouse (Lazarew 1929; Pantelitsch 1933), guinea pig (Price et al. 1978), cat (Lehmann 191 l), and monkey (Horiuchi et al. 1962) after acute- or intermediate-duration inhalation. Acute oral administration in rats also produced central nervous system depression and debilitation (Dow 1988). 1,1,2,2-Tetrachloroethane blocked avoidance learning when administered orally 30 minutes prior to testing (Wolff 1978). While it is assumed that these effects are those commonly found for volatile halocarbon solvents, there is no information about the specific site of action or mechanism of action in the nervous system.

Tests to show the site of action would be helpful in determining exactly how 1,1,2,2-tetrachloroethane affects the nervous system of humans. Also, a battery of neurofunction tests in animals would help identify the specific effects of the chemical and would evaluate the potential for long-term neurological effects in humans.

Epidemiological and Human Dosimetry Studies. An epidemiological study was conducted analyzing the cancer mortality of service men exposed to 1,1,2,2-tetrachloroethane during World War II (Norman et al. 1981). The exposure was presumed to be mostly by inhalation, but dermal exposure was also possible and precise dosimetry was unknown. Over one thousand subjects were used in each of the control and exposed groups. There were only very slightly elevated incidences (not statistically significant) of cancer of the genital organs, as well as leukemia and lymphoma. It is possible that humans who live near hazardous waste sites may be exposed to this substance in the air, water, and soil. Additional epidemiological studies examining neurological effects and effects on the liver and kidney would be helpful to better define the effects of chronic-duration low-level exposures to 1,1,2,2-tetrachloroethane in humans.

Biomarkers of Exposure and Effect.

Exposure. Since the metabolites of 1,1,2,2-tetrachloroethane are known, and can be measured in the urine of rats (Yllner-1971), it is possible to measure these metabolites in urine to see if a person has been exposed to 1 ,1,2,2-tetrachloroethane. However, these metabolites are common to several types of chlorinated ethanes and would not be specific for exposure to 1,1,2,2-tetrachloroethane. Also, 1,1,2,2-tetrachloroethane is metabolized and excreted rather quickly, and the test might only indicate whether the person had been exposed in the last few days. Measurement of parent compounds and

metabolites in excreta or in biopsy samples (e.g., adipose), however, may allow quantitation of the body burden associated with exposures to known concentrations of 1,1,2,2-tetrachloroethane.

Effect. 1,1,2,2-Tetrachloroethane may cause liver damage. In cases where humans have been exposed to high levels of 1,1,2,2-tetrachloroethane, it may be possible to correlate urinary metabolites with serum indicators of liver malfunction, although the metabolites would not be specific for 1,1,2,2-tetrachloroethane.

Absorption, Distribution, Metabolism, and Excretion. In both humans (Morgan et al. 1970; Lehmann and Schmidt-Kehl 1936) and laboratory animals (Dow 19SS), 1,1,2,2-tetrachloroethane is well absorbed after acute-duration inhalation exposure. While studies in which the quantitation of absorption following oral exposure was measured in humans were not available, the profound effects following ingestion of 1,1,2,2-tetrachloroethane indicate that appreciable amounts are absorbed by this route also. This is consistent with the data from animal studies, which indicate that oral doses are mostly absorbed (Milman et al. 1984; Mitoma et al. 1985). No studies were located regarding absorption following dermal exposure in humans. Only limited information was found regarding the distribution of 1,1,2,2-tetrachloroethane following inhalation, oral, or dermal exposure in humans and animals. High levels of binding of 1,1,2,2-tetrachloroethane equivalents to hepatic proteins were found in rats and mice following oral dosing. 1,1,2,2-Tetrachloroethane is extensively metabolized in animals and excreted chiefly as metabolites in urine and breath (Ikeda and Ohtsuji 1972; Mitoma et al. 1985; Yllner 1971).

Modem techniques employing mass spectrometry and/or nuclear magnetic resonance coupled with high resolution chromatographic methods to provide unambiguous structural identification were used only in a few recent studies. Unfortunately, the emphasis in those studies was the elucidation of particular mechanisms of reactive intermediate metabolite formation. A more broadly based evaluation of the formation of nontoxic or less toxic metabolites was not fully pursued. Fuller studies, such as that of Yllner (1971), employed less rigorous characterization methodology and structural assignments of metabolites made are not definitive. Metabolic pathways, and rates and patterns of distribution and excretion may be different following oral exposure than following inhalation or dermal exposure. Differences in metabolism may account for differences in toxicity following exposure by these routes. Thus, further studies in animals of the rate and extent of absorption and excretion, of distribution, and of metabolism following exposure by all three routes, and in vitro studies to elucidate metabolic

pathways, would provide the information to fully characterize the pharmacokinetics of 1,1,2,2-tetrachloroethane in animals.

Comparative Toxicokinetics. Physiologically based-pharmacokinetic modeling of the kinetics of 1,1,2,2-tetrachloroethane in rats exposed by inhalation has been performed by Gargas and Anderson (1989). Data on comparative toxicokinetics in rats and mice exposed to 1,1,2,2-tetrachloroethane by intermediate-duration inhalation exposure are available (Mitoma et al. 1985). Mice metabolized 1,1,2,2-tetrachloroethane at roughly twice the rate of rats given similar doses, and the amount of protein bound equivalents were higher. Further studies in these and other species may provide information to account for differences in toxicity among animal species. There are limited human metabolism and excretion data. A single study has shown that 3% of inhaled 1,1,2,2-tetrachloroethane was excreted in the breath, and that the urinary excretion rate was 0.015% absorbed dose/minute (Morgan et al. 1970). Analysis of levels of metabolites in the urine of people with known exposure could provide knowledge of metabolic pathways in humans. Additionally, biochemically viable human tissues, including liver, are now routinely available for metabolism studies. In this way, the metabolism of 1,1,2,2-tetrachloroethane in humans of differing genetic background and life style (e.g., consumers of alcohol or tobacco) can be determined in microsomes and precision-cut tissue slices. This information may allow accurate prediction of the metabolism of 1,1,2,2-tetrachloroethane in humans. Qualitative comparisons of human metabolites with those of animals could help to identify the most appropriate animal species to serve as a model for predicting toxic effects in humans and studying the mechanism of action.

Methods for Reducing Toxic Effects. No studies were located regarding the mechanism of absorption in humans or animals after inhalation, oral, or dermal exposure to 1,1,2,2-tetrachloroethane. Carbon and castor oil have been shown to increase the survival times in rats administered oral doses of 1,1,2,2-tetrachloroethane (Laass 1973a, 1973b, 1974a, 1974b), but data are needed on the actual mechanisms of absorption and distribution of this chemical in the body. 1,1,2,2-Tetrachloroethane is metabolized to reactive toxic acyl chlorides and to free radicals. No treatments were described that mitigate the health effects that result from exposure to the compound. However, alcohol and acetone, inducers of cytochrome P-450 isoenzyme 2El increased the metabolism of 1,1,2,2-tetrachloroethane and intensified the toxic effects (Gohlke and Schmidt 1972; Sato et al. 1980). Studies to determine methods for blocking the absorption or increasing the excretion of 1,1,2,2-tetrachloroethane would be helpful to better define methods to reduce the toxic effects of the chemical.

2.10.3 Ongoing Studies

1,1,2,2-Tetrachloroethane has been approved for toxicity and carcinogenicity testing by NTP (1988). The prechronic study has been completed, and is currently under review to determine whether further studies will be carried out. No ongoing biomonitoring studies were identified. No ongoing studies on the toxicokinetics of 1,1,2,2-tetrachloroethane were identified.